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CHAPTER I: INTRODUCTION TO BENZOTHIAZINES & BENZOSELENAZINES

The Chapter-I of the thesis will describe briefly about the introduction of benzothiazines, benzoselenazines, benzoxazines and benzothiazinones respectively.

Nitrogen containing six membered heterocycles play leading roles in the field of biological and medicinal chemistry.[1] These molecules have also been extensively used in the field of agrochemicals, pesticides, pharmaceuticals and in industries.[2] These molecules are also widely used as building blocks for bioactive molecules due to their immense pharmacological properties. The N-heterocyclic scaffolds containing oxygen or sulphur or selenium have found wide interest in the field of drug-discovery.[3] Among these N-heterocycles, benzothiazine and benzoselenazine derivatives are a unique class of compounds and have a larger scope towards the investigation of their novel biological activities. The medicinal properties of benzothiazines were investigated in detail from the time of development of cephalosporins.[4] Benzothiazine derivatives are known for their anti-inflammatory,[5] analgesic,[6] anticancer,[7] antiproliferative,[8] antibacterial,[9] and cardiovascular[10] activities. The selenium containing scaffolds like selenadiazoles[11] selenium-embedded polysaccharide protein complexes,[12] ebselen, seleno-chromenes[13] and benzoselenophene fused imidazopyridines[14] have received ample attention for their unique pharmacological properties. Similarly, a wide range of sulphur containing N-heterocycles have also been synthesized and found useful application in medicinal chemistry and drug discovery research.[15] On the other hand, the organo-selenium compounds are well-known for their antihypertensive,[16] antiviral,[17] anticancer,[18] antioxidant,[19] and antimicrobial properties.[20] The selenium containing drug ebselen has been widely explored by chemists due

to its valuable medicinal importance.[21] In recent years, chemists have described a considerable amount of research work on synthesizing selenium containing drugs.[22] Figures 1 and 2 represents various biologically active oxygen, sulphur and selenium embedded benzofused heterocycles.

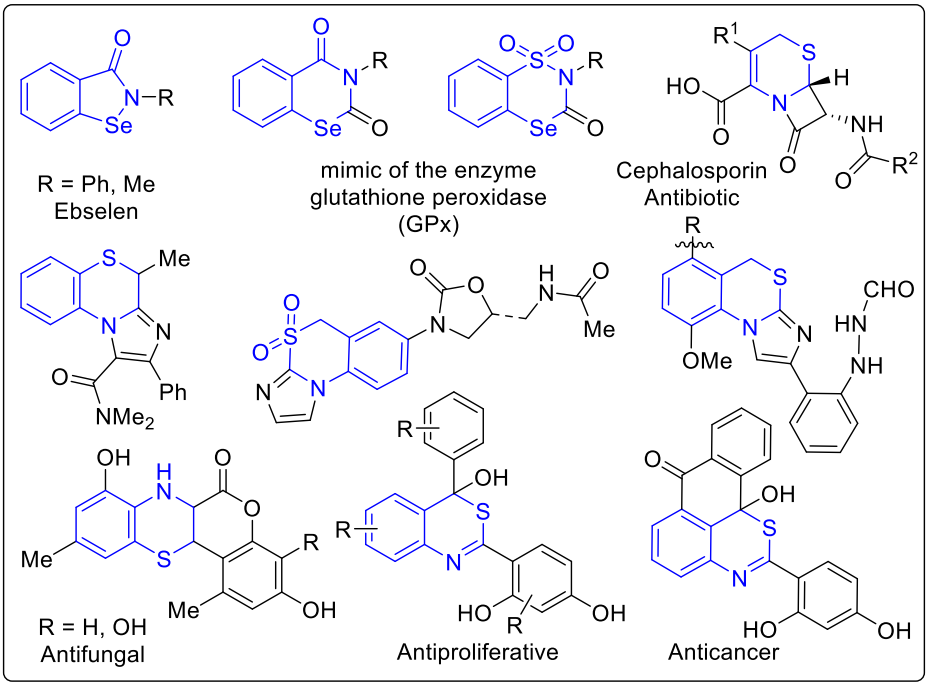


Figure 1: Biologically active oxygen, sulphur and selenium embedded benzofused heterocycles.

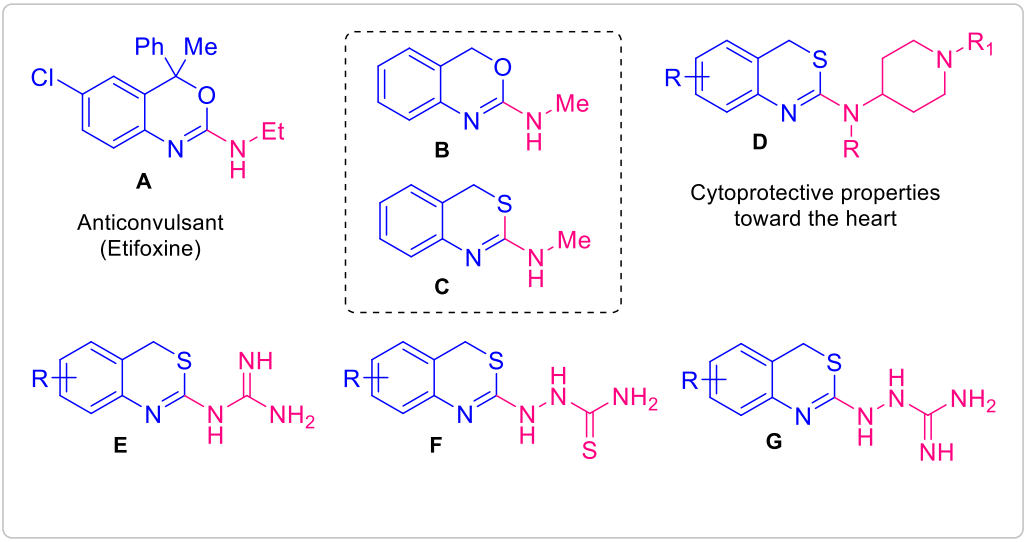


Figure 2: Pharmacological agents for the treatment of neurodegenerative pathologies.

4*H*-3,1-benzothiazin-4-ones with amino substituents at position 2 are representatives of a heterocyclic class that are assumed to possess biological activities since they might provide four heteroatoms as potential hydrogen bond acceptors and the fused phenyl ring for possible π-π interactions. Analogous 4*H*-3,1-benzoxazin-4-ones have attracted considerable attention as serine hydrolase inhibitors. Their interaction with serine hydrolases involves the acylation of the active-site serine due to enzymatic ring cleavage, followed by slow deacylation of the acyl-enzyme intermediate[23]. Biological activities of 4*H*-3,1-benzothiazin-4-ones and heterocyclic-fused analogues have been investigated less extensively[24]. But in the recent past the biological activity studies of 4*H*-3,1-benzothiazin-4-ones with amino substituents at position 2 have gathered pace. This is evident form the fact that they are identified as structurally novel antagonists of adenosine receptors (ARs)[25] and as well as Dual Targeting inhibitors of Adenosine A2A Receptors and Monoamine Oxidase B[26].

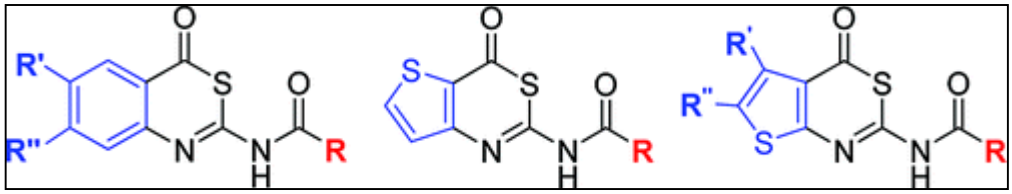


Figure 3: Novel antagonists of adenosine receptors.

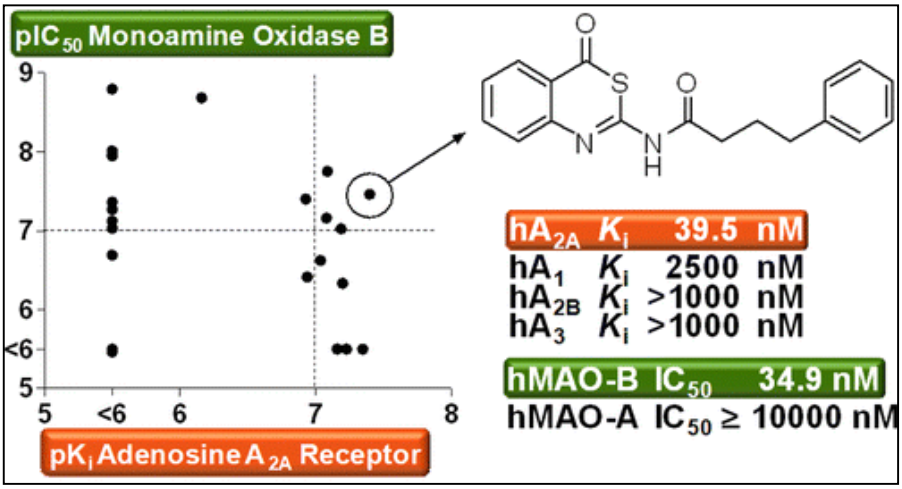


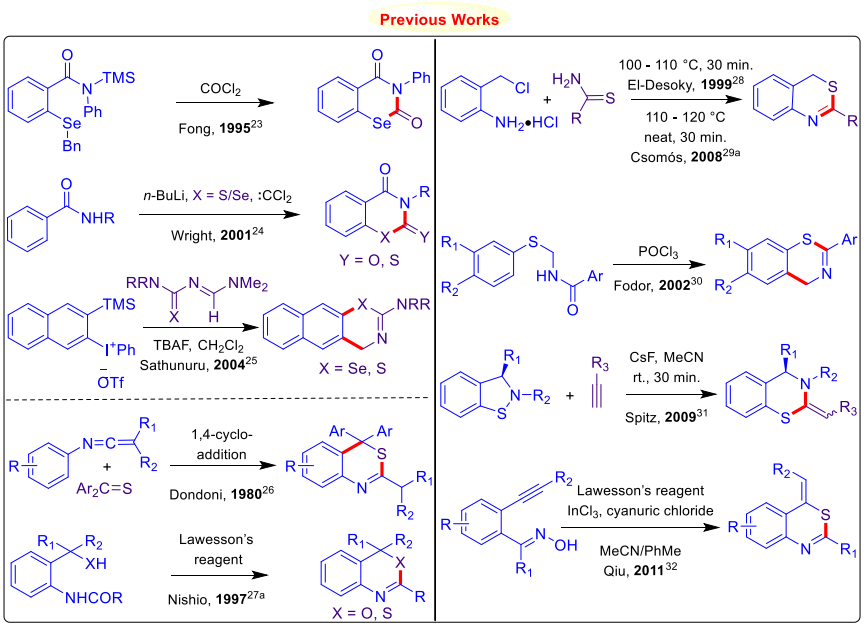
Figure 4: Dual Targeting inhibitors of Adenosine A2A Receptors and Monoamine Oxidase B.

CHAPTER-II: LITERATURE REVIEW

The Chapter-II of the thesis will describe briefly about the literature known methods for the synthesis of benzothiazines, benzoselenazines, benzoxazines and benzothiazinones respectively.

2.1 Literature review of 2-substituted 1,3 Benzothiazines and 2-substituted 1,3 Benzoslenazines:

According to the literature survey, the previously reported methods for the preparation of 1,3-benzoselenazines and 1,3- benzothiazines are highlighted in Scheme 1. Fong and coworkers[27] have described the synthesis of 3-phenyl-1,3(4H)-benzoselenazine-2,4(3H)-dione using complex amide substrates under hazardous conditions. Wright[28] has developed a protocol for the synthesis of benzo[e][1,3]selenazine-2,4-dione by sequential reactions of benzamide under n-BuLi mediated reaction conditions. Sathunuru and his coworkers[29] have developed a route towards the synthesis of 4H-naphtho[2,3-e]-1,3-selenazines from heir corresponding selenazadienes and 2,3-didehydronaphthalene.



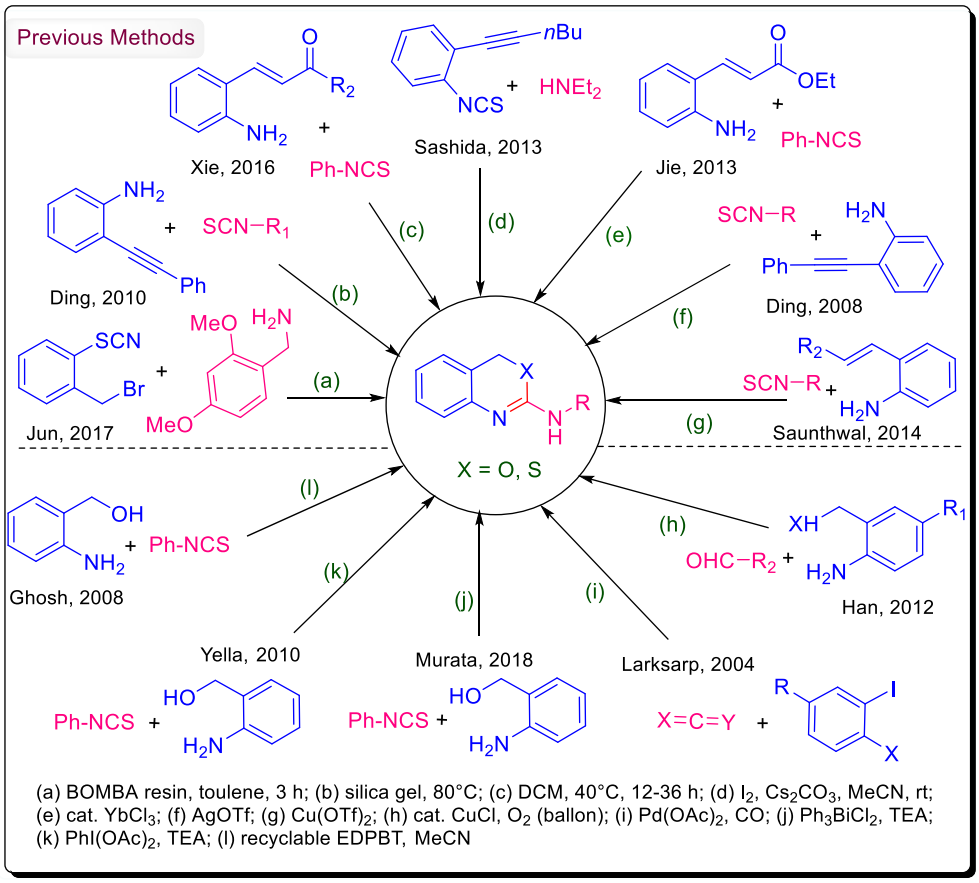
Scheme 1: Previous reports for the synthesis of 1,3-benzoselenazines and 1,3-benzothiazines

It is noteworthy that all the reported previous methods suffer from unfavorable reaction conditions like the formation of benzyne intermediates, and the usage of carcinogenic reagents like phosgene, and n-BuLi. The reported methods also rely on the low yield and narrow scope of 1,3-benzoselenazines. Similarly, the reported methods towards the preparation of 1,3-benzothiazines have also been surveyed. It has been found that a number of notable and useful methods were developed by Dondoni,[30] Nishio,[31] El-Desoky,[32] Csomós,[33] Fodor,[34] Spitz,[35] and Qiu[36] (Scheme 1). Apart from the above-mentioned protocols, Taylor[37] and Wang[38] have also reported several methods for the synthesis of fused 1,3-benzothiazines

2.2 Literature review of 2-amino substituted 1,3 Benzothiazines and 2-amino substituted 1,3 Benzoxazines:

A spectrum of methods had been developed for the synthesis of 1,3-benzoxazines and 1,3-benzothiazines. Among the traditionally used protocols, the most commonly attempted approaches are (i) metal-catalyzed tandem addition-cyclzation reactions and oxidative synthesis,[39, 40] (ii) non-metal catalyzed/dehydrosulfurization methods,[41] and (iii) non-catalytic approaches.[42] A summary of the previously reported procedures towards the preparation of 1,3-benzoxazines and 1,3-benzothiazines are presented in Scheme 2. Jie and co-workers have achieved an one-step synthesis of 2-amino-4*H*-1,3-benzothiazines *via* $YbCl_3$-catalyzed tandem addition-cyclization reaction of *o*-aminocinnamate and isothiocyanates (Scheme 2e).[39] The similar transformation has also been achieved by Ding et al under silver-catalyzed tandem addition-cyclization reactions of 2-alkynylbenzenamines with isothiocyanates (Scheme 2f).[40] Saunthwal et al described the synthesis of these scaffolds by the reaction of 2-aminoaryl acrylates with isothiocyanates *via in-situ* thioamidation and concomitant chemoselective intramolecular thia-michael addition (Scheme 2g).[40] Han and co-workers have reported an efficient method towards 1,3-benzoxazines by the reaction

between aldehydes and 2-aminobenzylamines or 2-aminobenzyl alcohols *via* an aerobic oxidative synthesis in the presence of Cu-catalyst (Scheme 2h).[40] A cyclocarbonylation reaction of *o*-iodoanilines with hetero-cumulenes was demonstrated by Larksarp and co-workers to afford the synthesis of 1,3-benzoxazines (Scheme 2i).[40] Various non-catalytic conditions were also reported for the synthesis of these molecules, those include tandem addition-cyclization reactions of 2-alkynylbenzenamines with isothiocyanates promoted by silicagel (Scheme 2b).[40]



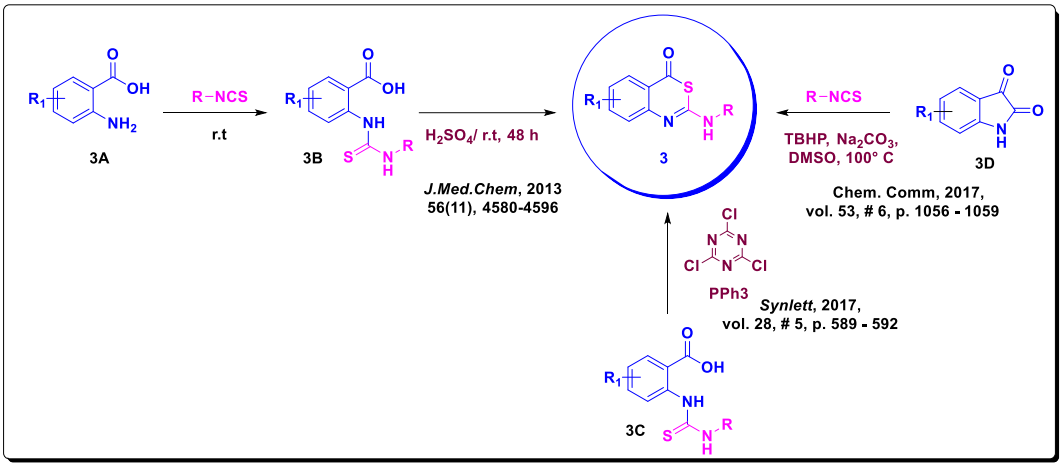
Scheme 2: Approaches towards the synthesis of 1,3-benzoxazine and 1,3-benzothiazines

The reaction of 2-amino chalcones with isothiocyanates could also deliver these molecules (Scheme 1c),[42] and recently, Jun and co-workers have described a microwave-assisted solid-phase synthesis of 1,3-benzothiazines using BOMBA Resin as support (Scheme 2a). [42] In addition, the metal-free approaches for the synthesis of 1,3-benzothiazines have been

achieved by the reaction between *o*-ethynylphenyl isothiocyanates and primary or secondary amines.[42] The reaction was catalyzed by molecular iodine to accomplish the transformation (Scheme 2d). Moreover, these scaffolds were constructed by dehydrosulfurization method by the reaction between 2-amino benzylalcohols and isothiocyanates using $PhI(OAc)_2$ and EDPBT as the reagents (Scheme 2k-l).[41]

2.3 Literature review of 2-amino substituted 1,3 Benzothiazinones and 2-amino substituted 1,3 Benzoxazines:

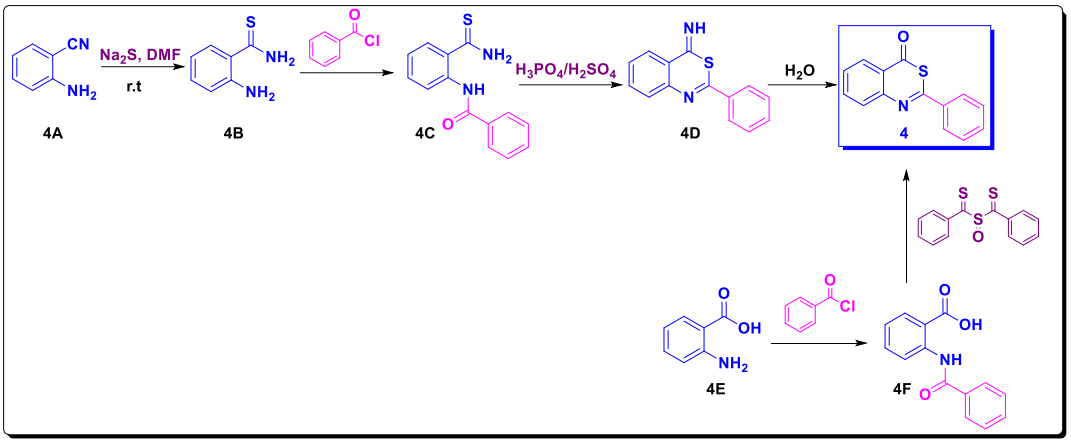
2- Amino substituted benzothiazinones have been traditionally synthesized starting from the corresponding anthranilic acids, which are converted to the corresponding thioureas and then treated with either sulphuric acid or cyanuric chloride at higher temperatures to yield the 2-amino benzothiazinones. Alternatively, a one pot methodology has been recently developed using TBHP and sodium bicarbonate starting from Isatins to yield the corresponding benzothiazinones.



Scheme 3: Synthesis of 2-amino- and 2-alkylthio-4*H*-3,1-benzothiazin-4-ones.

2-Cyano anilines are initially converted to thiobenzamides followed by arylation at the amine, cyclization and hydrolysis yields the 2-aryl benzothiazinones. Alternatively, bis-1,3-Benzenediol, 4,4'-(sulfinyldicarbonothioyl) are prepared by a twostep process and then reacted

with 2-aminobenzyl alcohols in MeOH to yield the corresponding 2-aryl benzothiazinones.



Scheme 4. Synthesis of 2-aryl-4*H*-3,1-benzothiazin-4-ones.

2.4.1 Aim and Objective:

- To develop mild, efficient and simple synthetic methodology for Benzothiazenones and Benzothiazines
- To expand the developed methodology to the corresponding selenium derivatives
- To screen and identify suitable dehydrating reagent to develop one-pot / one step methodology
- To generalize the reaction conditions and expand the substrate scope to aliphatic and acid sensitive substrates
- To screen the synthesized compounds for their antibacterial activities

CHAPTER-III: 2-SUBSTITUTED 1,3 BENZOTHIAZINES & SALENAZINES

This chapter describes the introduction, results, discussion and conclusion for the synthesis of 2-substituted 1,3 benzothiazines & selenazines.

3.1 Introduction

Efficient protocols have been described for the synthesis of 1,3-benzoselenazines, 1,3-benzothiazines, 2-aryl thiazin-4-ones and diaryl[b,f][1,5]diazocine-6,12(5H,11H)-diones. These transformations were successfully driven towards the product formation under mild acid catalyzed reaction conditions at room temperature using 2-amino aryl/hetero-aryl alkyl alcohols and amides as substrates. The merits of the present methods also rely on the easy access of rarely explored bioactive scaffolds like 1,3-benzoselenazine derivatives, for which well-documented methods are rarely known in the literature. A broad range of substrates with both electron-rich and electron-deficient groups were well-tolerated under the developed conditions to furnish the desired products in yields up to 98%. The scope of the devised method is not only restricted to the synthesis of 1,3-benzoselenazines, but it was also further extended towards the synthesis of 1,3-benzothiazines, 1,3-benzothiazinones and the corresponding eight membered N-heterocycles such as diaryl[b,f][1,5]diazocine-6,12(5H,11H)-diones.

3.2 Results and Discussion

To start with the initial experiments, the corresponding arylselenocarboxamides[35] 2a–h and arylthiocarboxamides[36] were synthesized using literature known methods. 2-aminobenzylalcohol (1a) and phenyl selenocarboxamide (2a) as our model substrates and the reactions

were carried out using various reagents, solvents and the results are depicted in the below table (Table 1).

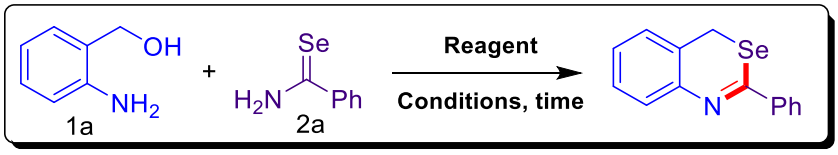
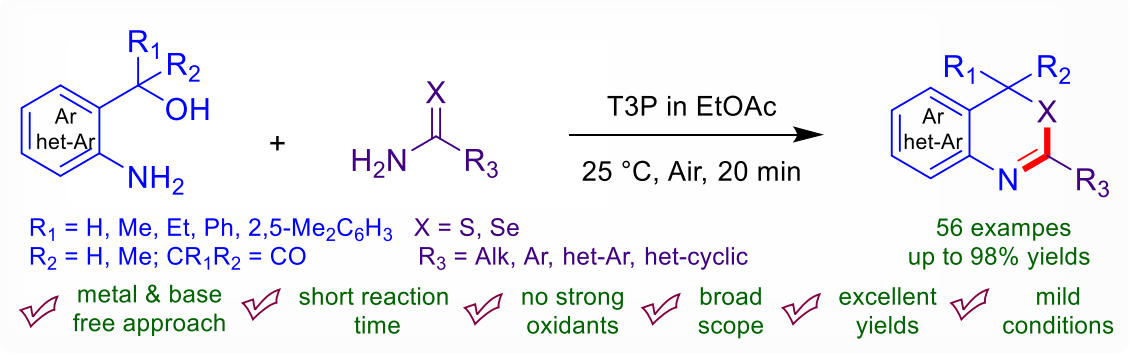
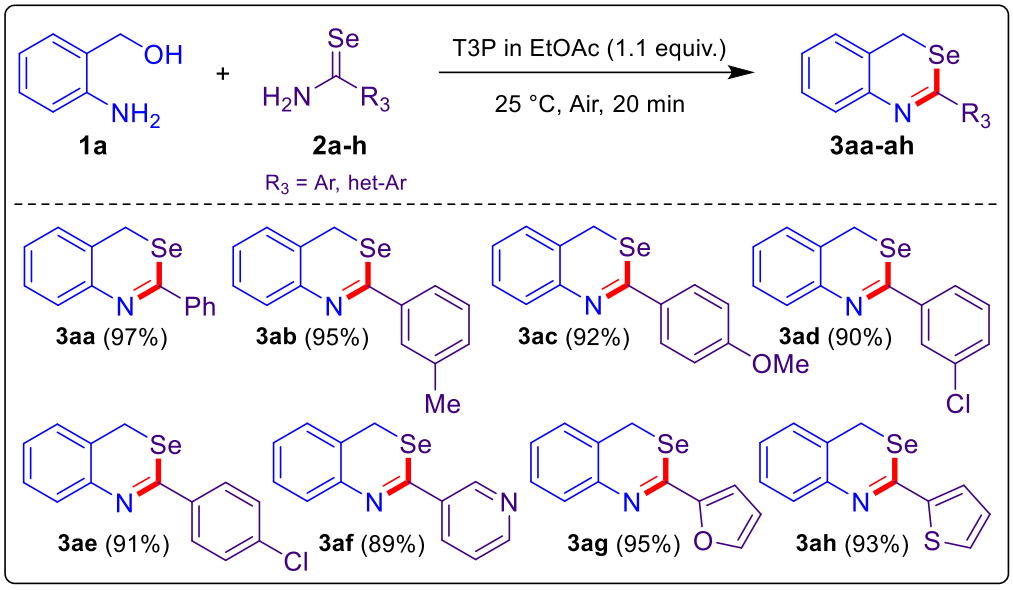


Table 1: Screening of the conditions for the reaction between 1a and 2a

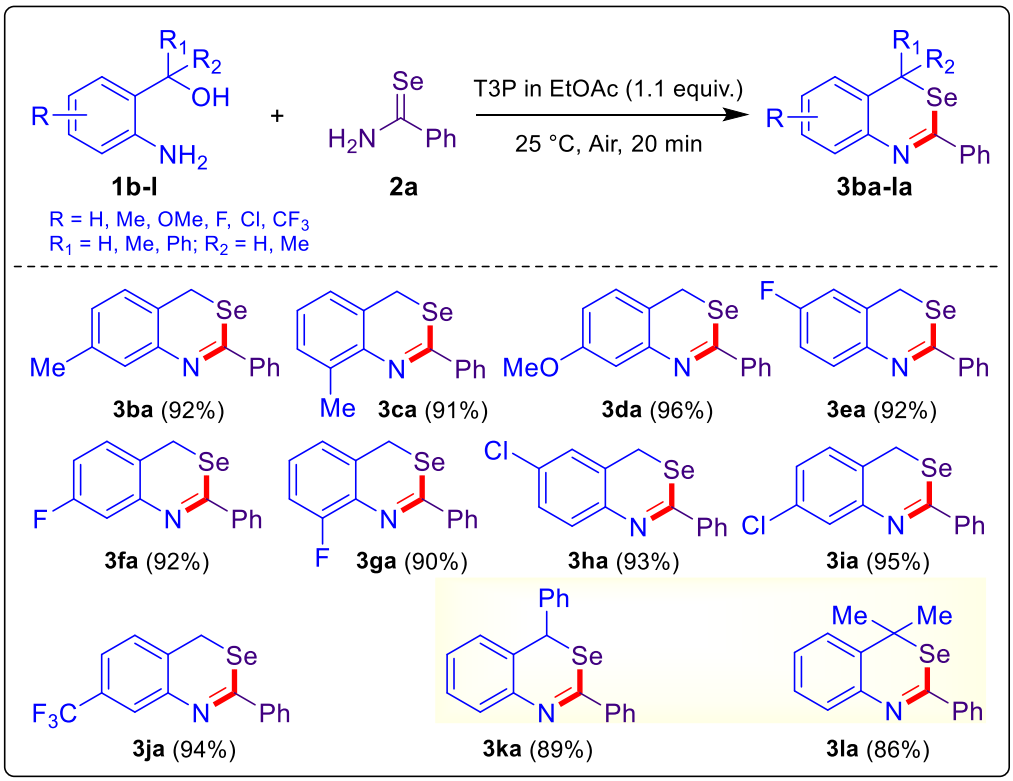
Entry	Reaction conditions	3aa, % yield[b] (% conversion)[c]
1	EDC·HCl (1.1 equiv.), MeCN	0 (<25)
2	DCC (1.1 equiv.), MeCN	0 (<25)
3	BOP (1.1 equiv.), MeCN	0 (<25)
4	PyBOP (1.1 equiv.), MeCN	0 (<25)
5	HATU (1.1 equiv.), MeCN	0 (<25)
6	HOBt (1.1 equiv.), MeCN	0 (<25)
7	I_2 (1.1 equiv.), MeCN	17 (<50)
8	T3P (1.1 equiv.), MeCN	91 (100)
9	T3P (1.1 equiv.), THF	89 (100)
10	T3P (1.1 equiv.), DCM	85 (100)
11	**T3P (1.1 equiv.), Neat**	**97 (100)**
12	T3P (0.5 equiv.), Neat	78 (92)
13	T3P (1.5 equiv.), Neat	96 (100)
14	T3P (1.1 equiv.), Et_3N (3.0 equiv.), Neat	42 (75)

All reactions were performed using 1 mmol of 1a and 1 mmol of 2a in 2 mL solvent at room temperature (25 °C) for 20 minutes. T3P anhydride solution ≥50 wt% in ethyl acetate was used. [b] Isolated yields. [c] Conversion into 3aa.

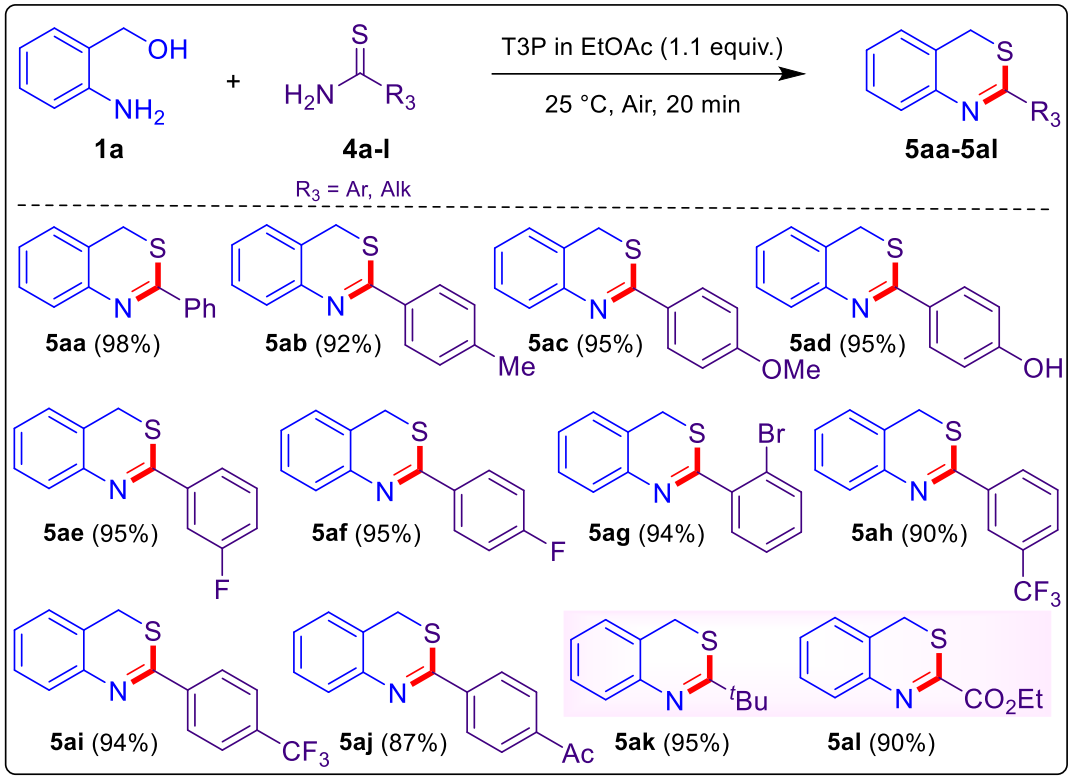




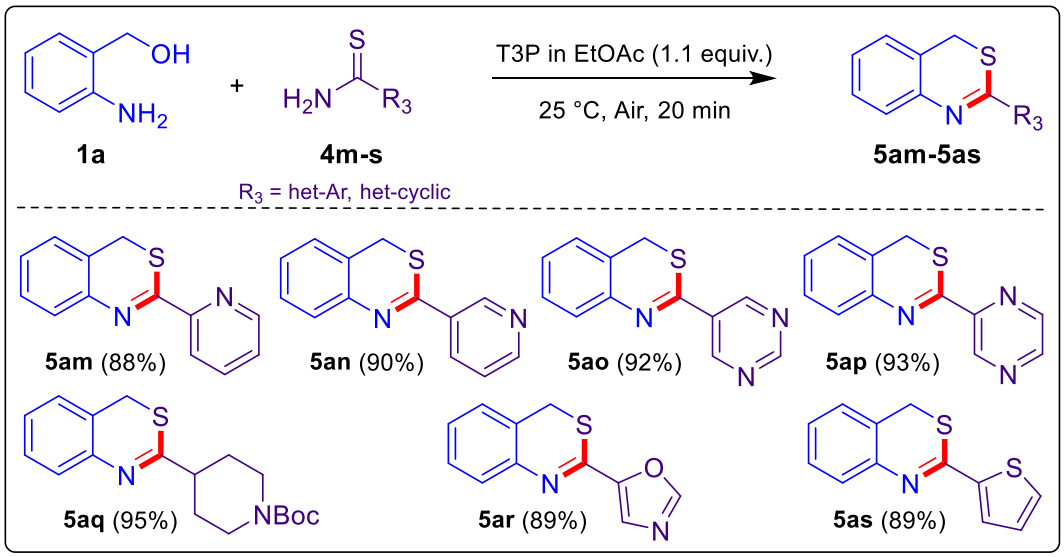
Scheme 5: Synthetic scope of the 1,3-benzoselenazines under the developed conditions using aromatic and hetero-aromatic amides.



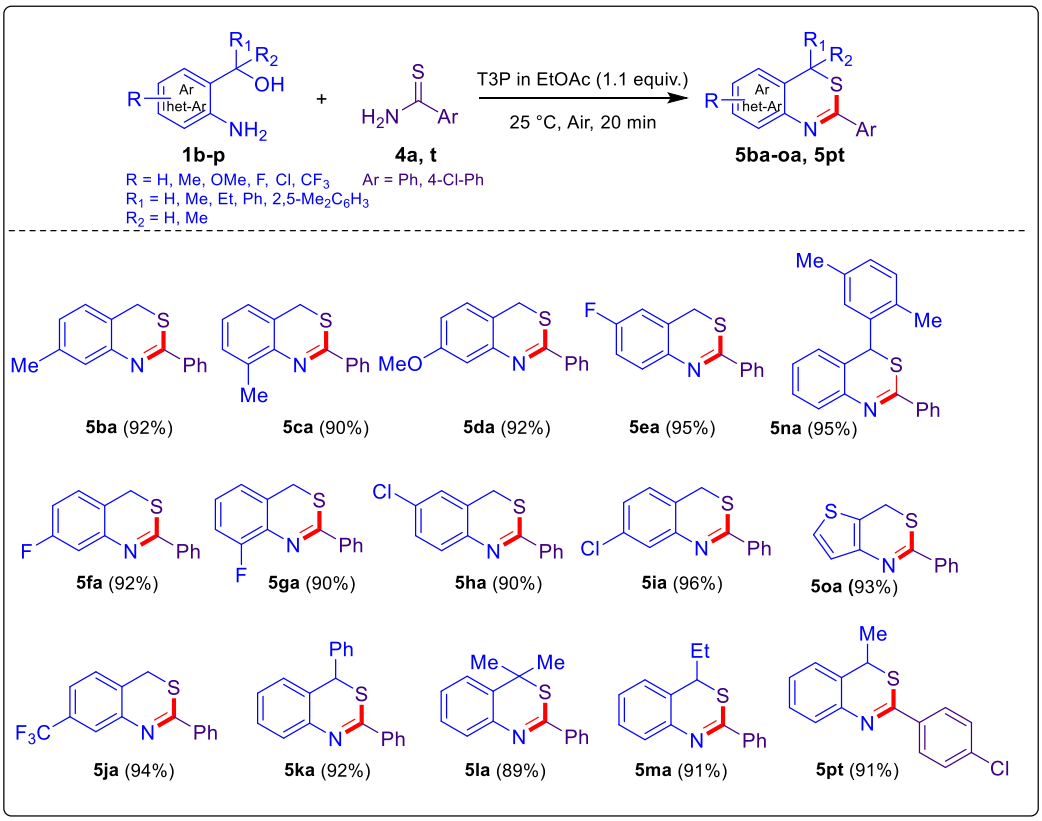
Scheme 6: Scope of 1,3-benzoselenazines using various benzylalcohols.



Scheme 7: Reactivities of aromatic and aliphatic amides for the preparation of 1,3-benzothiazines.

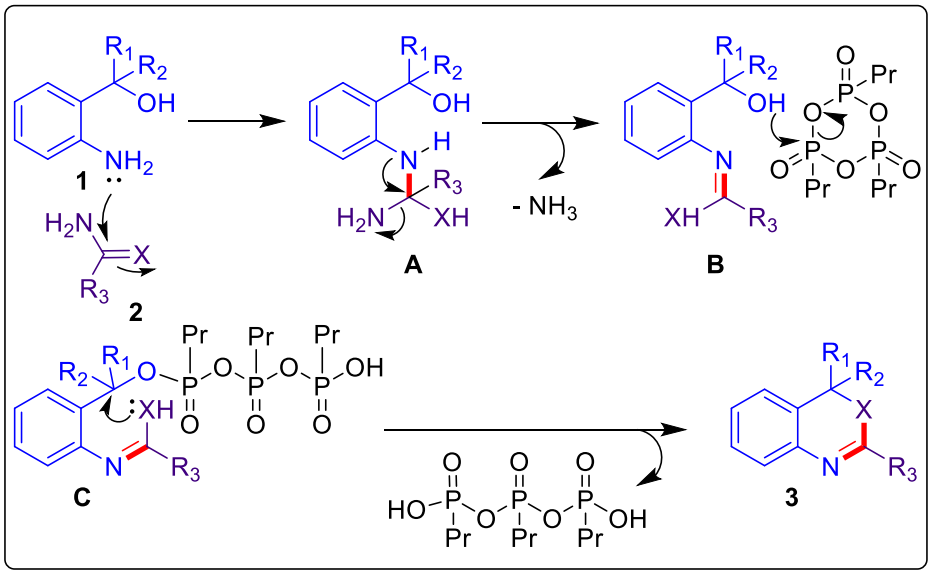


Scheme 8: Synthesis of 1,3-benzothiazines using hetero-aromatic amides.



Scheme 9: Synthesis of 1,3-benzothiazines using different aryl–alkyl alcohols.

3.2.1 Plausible reaction mechanism:



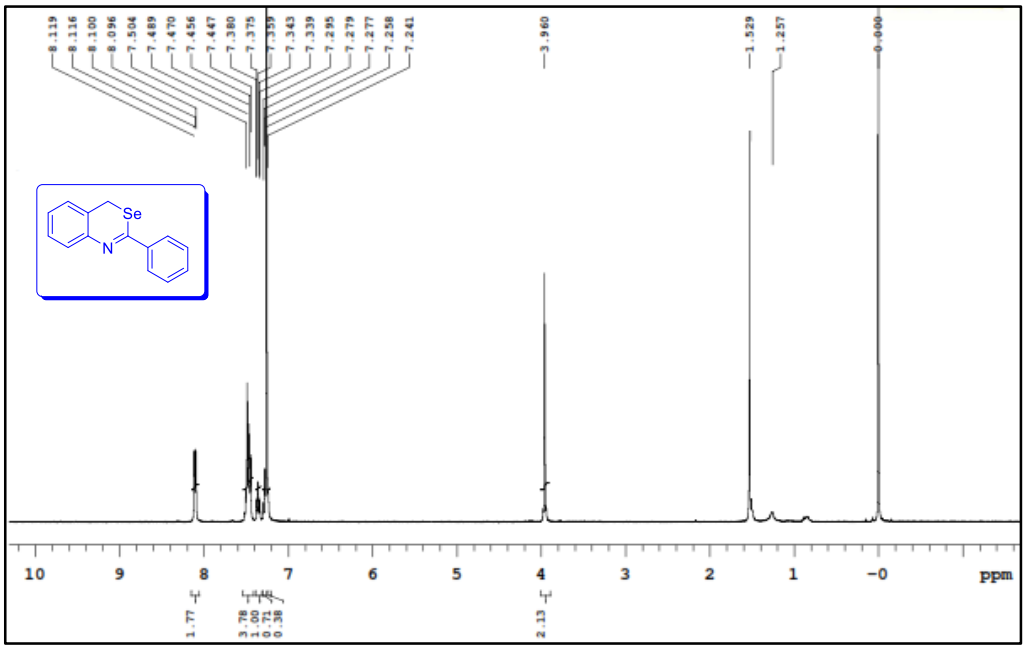
Scheme 10: Plausible reaction mechanism for the formation of 1,3 benzoselenazines and 1,3-benzothiazines.

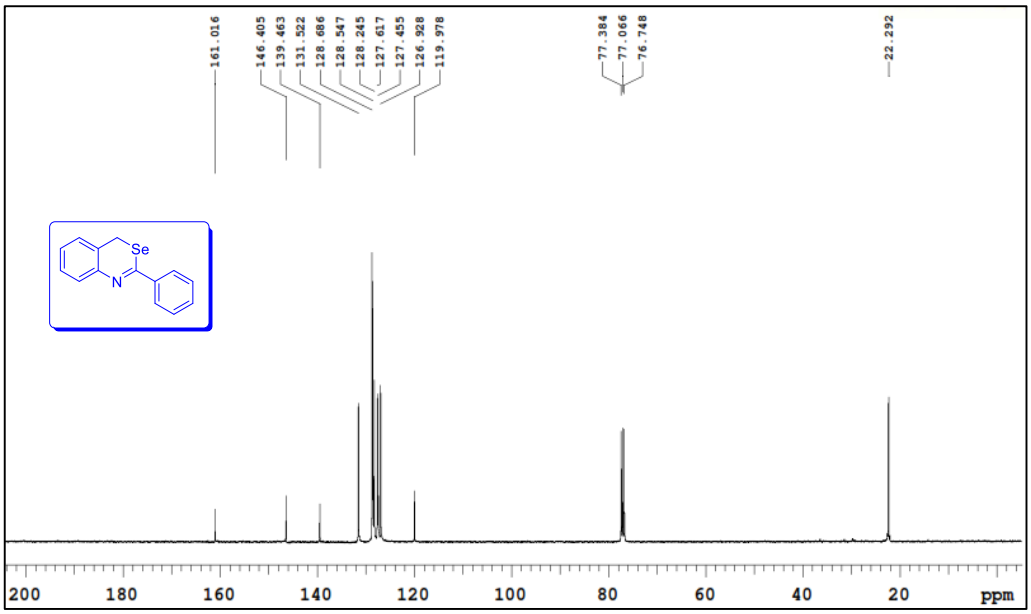
The nucleophilic attack of amine 1 on the amide 2 takes place to give the corresponding intermediate A. Subsequently, the elimination of ammonia from intermediate A gives the imine intermediate B. Furthermore, the nucleophilic attack of the hydroxyl group of B on the phosphorus-atom of T3P would result in intermediate C. Finally, an intramolecular nucleophilic attack on T3P bound carbon delivers the desired product 3.

3.2.2 Spectral Data Analysis:

2-phenyl-4H-benzo[d][1,3]selenazine (3aa)

2-aminobenzyl alcohol **1a** (1.0 mmol, 123 mg), benzoselenoamide **2a** (1.0 mmol, 184 mg), T3P (1.1 mmol, 349.8 mg) were reacted to obtain the desired 2-phenyl-4H-benzo[d][1,3]selenazine **3aa** in 97% (265 mg) yield as pale yellow solid.





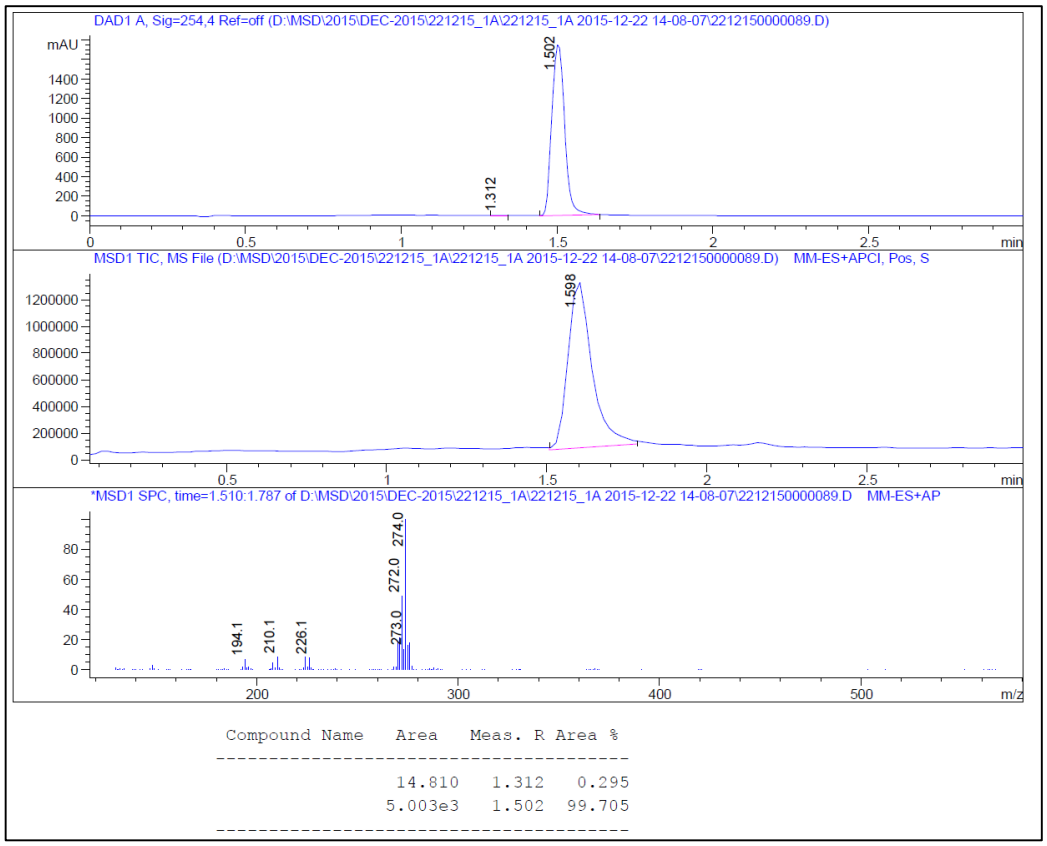
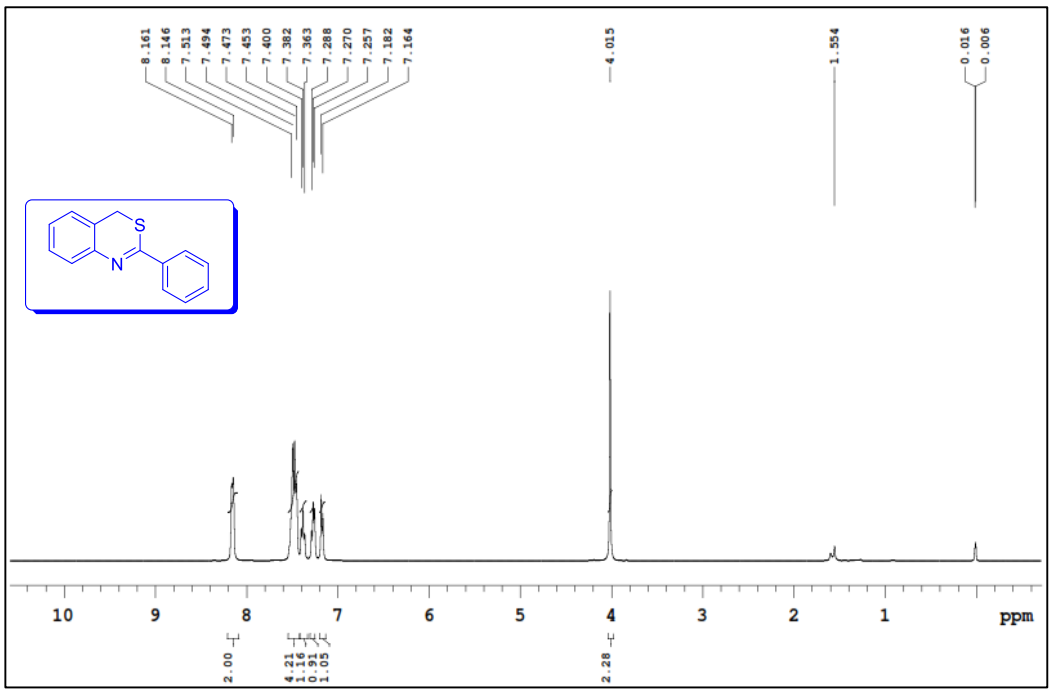


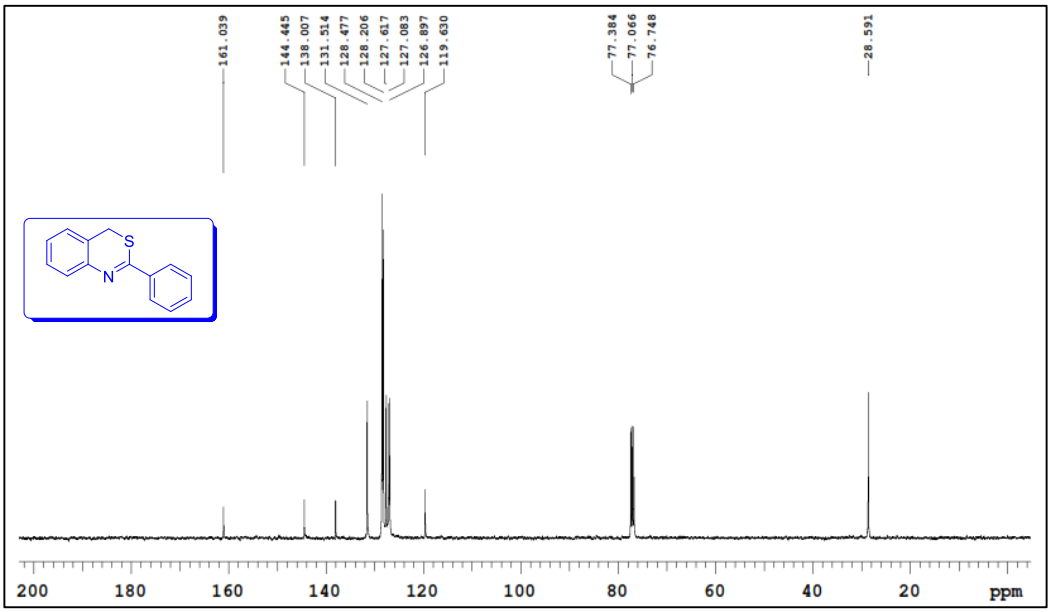
Figure 5. ^{1}H (400 MHz), ^{13}C (100 MHz) NMR spectra of 3aa in $CDCl_3$ and LC-MS in Acetonitrile.

Pale yellow solid; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.10 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.51 – 7.44 (m, 4H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.24 (m, 2H), 3.96 (s, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 161.0, 146.4, 139.4, 131.5, 128.6, 128.5, 128.2, 127.6, 127.4, 126.9, 119.9, 22.2 ppm; **MS** (APCI): $[M + 1]^+$ = 274.0 (99.70%); **HRMS** (ESI, $[M + H]^+$): calculated for $C_{14}H_{12}NSe$: 274.0134; found: 274.0130.

2-phenyl-4H-benzo[d][1,3]thiazine (5aa)

Reaction between 2-aminobenzyl alcohol **1a** (1.0 mmol, 123 mg), thiobenzamide **4a** (1.0 mmol, 137 mg), T3P (1.1 mmol, 349.8 mg) was performed to obtain the desired 2-phenyl-4H-benzo[d][1,3]thiazine **5aa** in 98% (221 mg) yield as white solid.





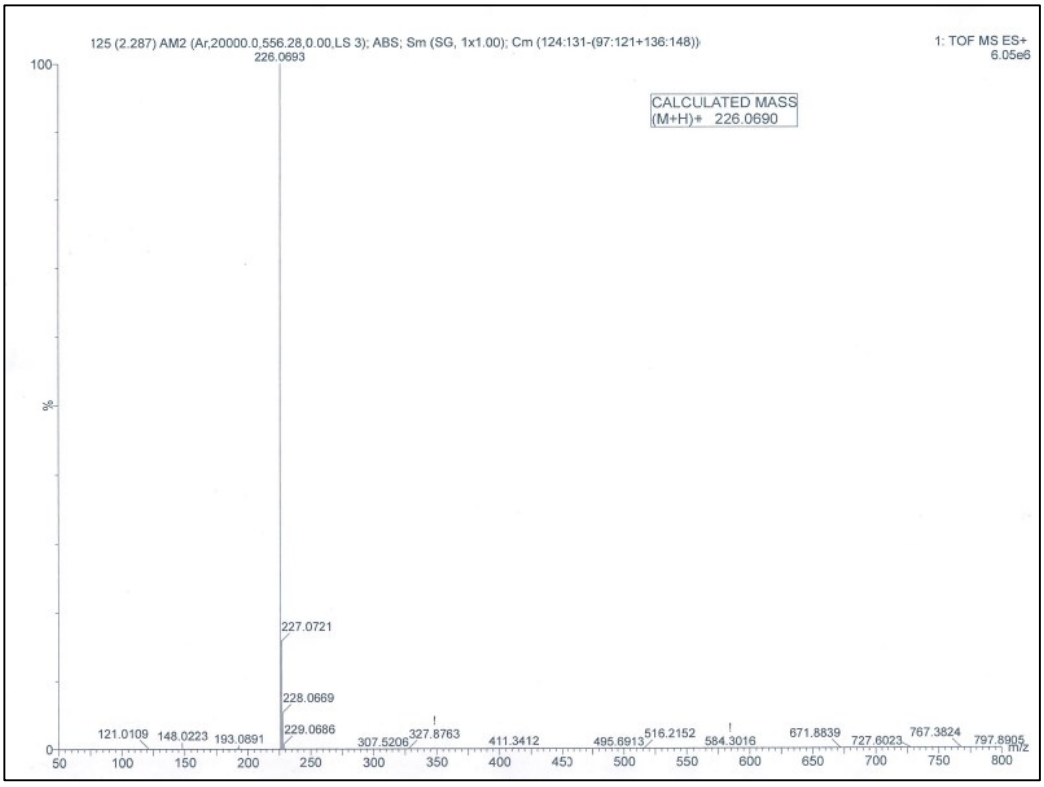


Figure 6.. ^{1}H (400 MHz), ^{13}C (100 MHz) NMR spectra of 5aa in $CDCl_3$ and HRMS in Acetonitrile.

White solid; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 95:5); **m.p** = 55 - 56 °C (Lit[1] 55 - 58 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 6.0 Hz, 2H), 7.51 - 7.45 (m, 4H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 4.00 (s, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) = δ 161.0, 144.4, 138.0, 131.5, 128.4, 128.2, 127.6, 127.0, 126.8, 119.6, 28.5 ppm; **HRMS** (ESI, $[M + H]^+$): calculated for $C_{14}H_{12}NS$: 226.0690; found: 226.0693.

3.3 Conclusion

In conclusion, we have developed a facile protocol for the synthesis of 1,3-benzoselenazines and 1,3-benzothiazines from aryl/heteroaryl-alkyl alcohols and selenocarboxamides or thiocarboxamides to obtain the desired products in excellent yields. The developed method was successful in overcoming the drawbacks associated with the previous reported protocols in terms of reaction conditions, substrates and the library of the products. All investigated examples proved to be general irrespective of the electronic nature of substituents on the substrates. The current protocol relies on the readily available inexpensive substrates under mild conditions at room temperature and minimum reaction time to synthesize a broad range of structurally diversified rarely explored 1,3-benzoselenazines and 1,3-benzothiazines.

CHAPTER-IV: 2-AMINO SUBSTITUTED 1,3 BENZOTHIAZINES & BENZOXAZINES

This chapter describes the introduction, results, discussion and conclusion for the synthesis of 2-amino substituted 1,3 benzothiazines & benzoxazines.

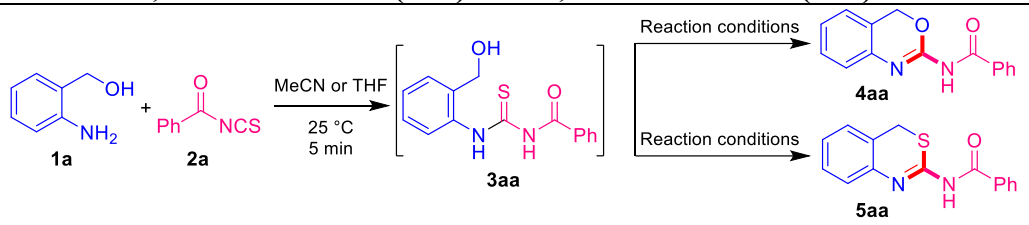
4.1 Introduction

The reported conditions for the synthesis of 2-amino substituted 1,3 benzothiazines & benzoxazines suffer from the disadvantages such as substrate scope, scalability and the long reaction times. Therefore, the development of an efficient and easy to access approach towards 2-amino-1,3-benzoxazines and 2-amino-1,3-benzothiazines using mild reaction conditions with less reaction time and at room temperature could be an useful tool in organic synthesis. In this regards, our attention drawn to the concept of molecular iodine assisted dehydrosulfurization for the synthesis of 1,3-benzoxazines, which is not much explored so far. Here, we reported two distinct reagent specific routes for the convenient preparation of 2-amino-1,3-benzoxazines and 2-amino-1,3-benzothiazines under mild reaction conditions and short reaction time.

4.2 Results and Discussion

To find the suitable experimental conditions for the dehydrosulfurization of thiourea intermediate (**3aa**), several reagents were tested. The intermediate (**3aa**) obtained from the reaction between 2-amino benzylalcohol (**1a**) and benzoyl isothiocyanate (**2a**) at room temperature, was reacted with molecular iodine / T3P in the presence of mild organic bases and different solvents at different temperatures.

Table 2: Screening of the reaction conditions towards the synthesis of 1,3-benzoxazines (4aa) and 1,3-benzoxazines (5aa).[a]



Entry	Reaction Conditions	**4aa**, % Yield[b] (% Conversion)[c]	**5aa**, % Yield[b] (% Conversion)[c]
1	I_2 (1.1 equiv.), DMAP (2 equiv.)	97 (100)	0
2	I_2 (1.1 equiv.), Pyridine (2 equiv.)	95 (100)	0
3	**I_2 (1.1 equiv.), Et_3N (2 equiv.)**	**98 (100)**	**0**
4	I_2 (1.1 equiv.), DIPEA (2 equiv.)	93 (100)	0
5	I_2 (1.1 equiv.), DBU (2 equiv.)	87 (100)	0
6	I_2 (1.1 equiv.), DABCO (2 equiv.)	81 (100)	0
7	I_2 (1.1 equiv.), NaO^tBu (2 equiv.)	17 (80)	0
8	I_2 (1.1 equiv.), KOH (2 equiv.)	< 10 (60)	0
9	I_2 (1.1 equiv.), *n*BuLi (2 equiv.)	63 (100)	0
10	I_2 (1.1 equiv.), LiHMDS (2 equiv.)	27 (100)	0
11	I_2 (1.1 equiv.), LDA (2 equiv.)	19 (100)	0
12	I_2 (1.1 equiv.)	0 (100)	0
13	Et_3N (2 equiv.)	0 (100)	0
14	NIS (1.1 equiv.), Et_3N (2 equiv.)	32 (50)	0
15	NBS (1.1 equiv.), Et_3N (2 equiv.)	18 (70)	0
16	I_2 (1.1 equiv.), Et_3N (2 equiv.), MeCN	57 (100)	0
17	I_2 (1.1 equiv.), Et_3N (2 equiv.), 1,4-dioxane	55 (100)	0
18	I_2 (1.1 equiv.), Et_3N (2 equiv.), PhMe	49 (60)	0
19	I_2 (1.1 equiv.), Et_3N (2 equiv.), DCM	68 (100)	0
20	I_2 (1.1 equiv.), Et_3N (2 equiv.), *i*PrOH	0 (0)	0
21	I_2 (1.1 equiv.), Et_3N (2 equiv.), H_2O	0 (0)	0
22	I_2 (0.5 equiv.), Et_3N (2 equiv.)	38 (50)	0
23	I_2 (1.5 equiv.), Et_3N (2.5 equiv.)	97 (100)	0

24	**T3P (1.1 equiv.), Et_3N (2.2 equiv.), MeCN**	**trace**	**95 (100)**
25	T3P (1.1 equiv.), Et_3N (2.2 equiv.), THF	< 5	78 (100)
26	T3P (1.1 equiv.), Et_3N (2.2 equiv.), DCM	< 5	81 (100)
27[d]	T3P (1.1 equiv.), Et_3N (2.2 equiv.)	< 5	69 (100)
28	EDC·HCl (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
29	DCC (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
30	BOP (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
31	PyBOP (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
32	HATU (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0

[a]Unless otherwise indicated: The reactions were performed using 1.0 mmol **1a**, 1.0 mmol **2a** in 2 mL THF at room temperature (25 °C) for 5-20 minutes (Entries 1-15, 22-23). The reactions were performed using 1.0 mmol **1a**, 1.0 mmol **2a** in 2 mL of MeCN at room temperature (25 °C) for 5-20 minutes (Entries 24-32). T3P anhydride solution ≥50 wt. % in ethyl acetate was used. [b]Isolated yields. [c]Conversion into product was monitored by LC-MS. [d]Rection was carried out without solvent.

A Detailed optimization study (Table 2) showed that the highest yield of the product 1,3-benzoxazine (4aa) was obtained when the conversion of intermediate 3aa was performed in the presence of 1.1 equiv. molecular iodine and 2.0 equiv. of Et_3N in THF as solvent at room temparature (25 °C) for 5-20 minutes (Table 1, Entry 3). Consequently, the corresponding product 1,3-benzothiazine (5aa) was obtained in maximum yield when the reaction was performed using 1.1 equiv. of T3P as cyclodehydrating agent and 2.2 equiv. of Et_3N at room temperature (25 °C) for 5-20 minutes (Table 2, Entry 24).

Having the optimal results, initially we explored the scope of the reaction by employing the various 2-amino-aralkyl alcohols (**1a-l**) with

benzoyl isothiocyanate (**2a**) to obtain the desired products 2-amino-1,3-benzoxazines

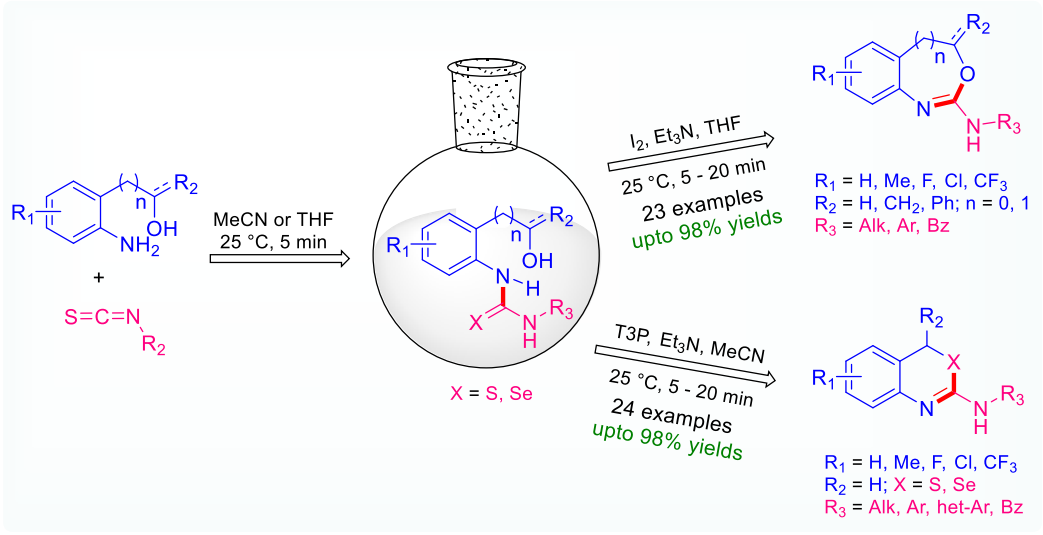
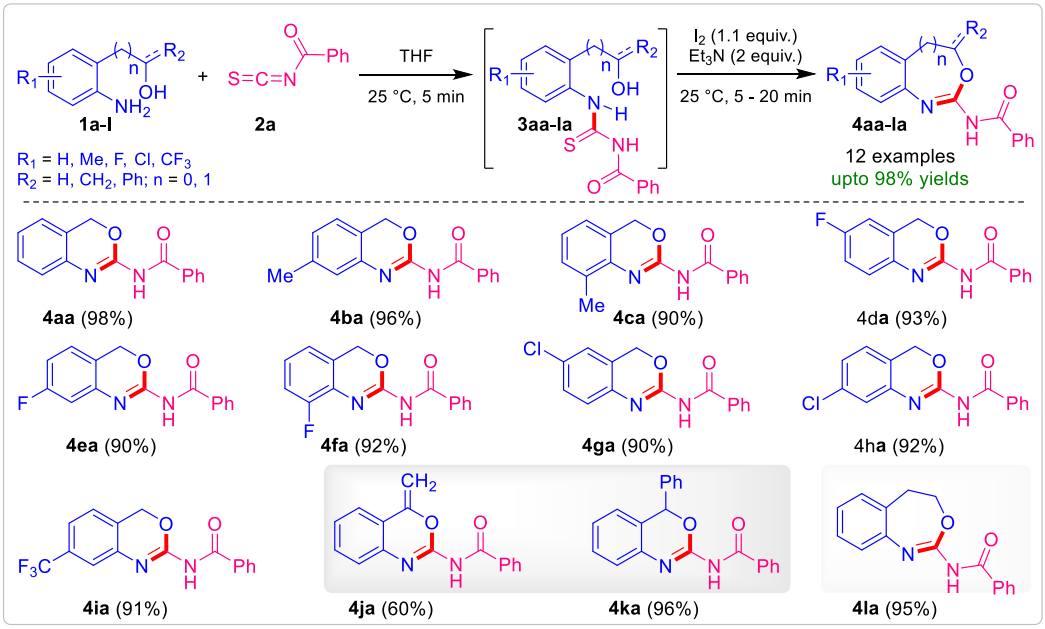
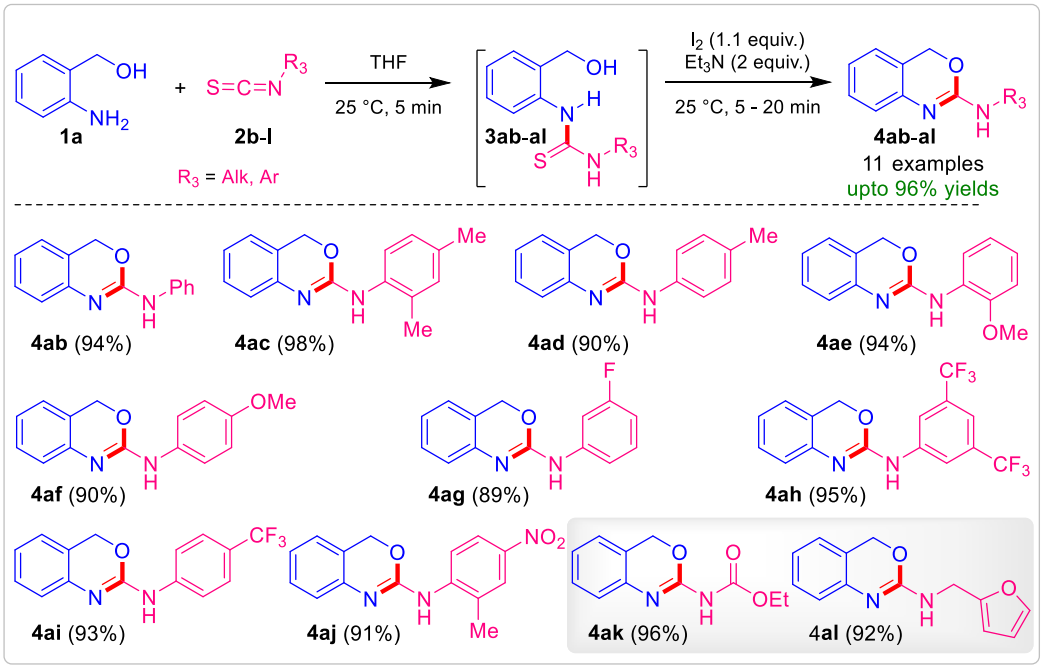

MeCN or THF
25 °C, 5 min
X = S, Se
I2, Et3N, THF
25 °C, 5 - 20 min
23 examples
upto 98% yields
R1 = H, Me, F, Cl, CF3
R2 = H, CH2, Ph; n = 0, 1
R3 = Alk, Ar, Bz
T3P, Et3N, MeCN
25 °C, 5 - 20 min
24 examples
upto 98% yields
R1 = H, Me, F, Cl, CF3
R2 = H; X = S, Se
R3 = Alk, Ar, het-Ar, Bz

Figure 7: Optimized condition for synthesis of 2-amino substituted 1,3 benzothiazines & benzoxazines

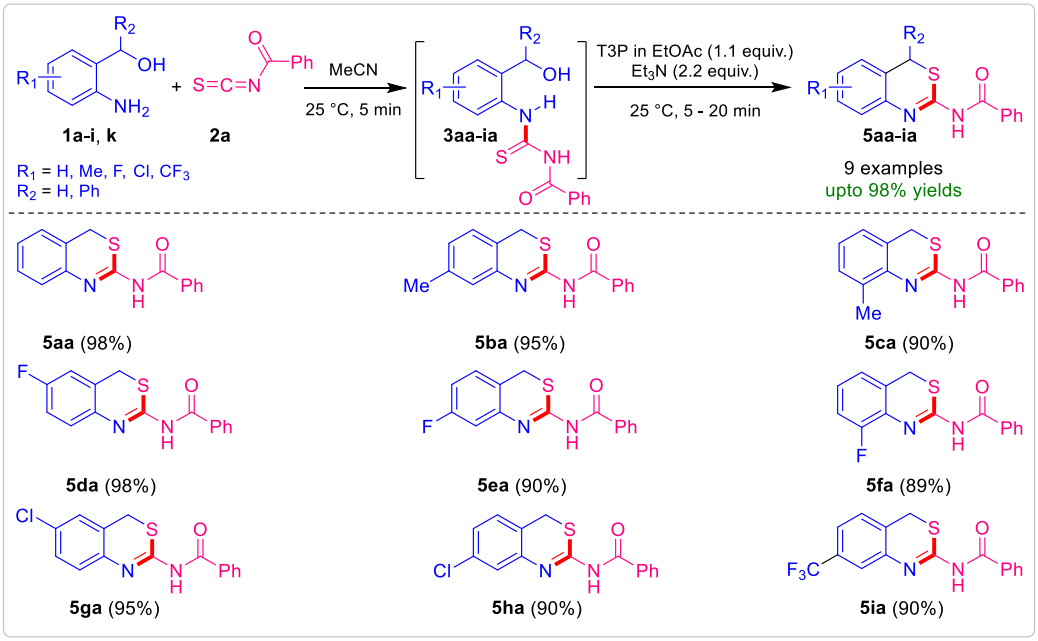


Scheme 11: Synthesis of 1,3-benzoxazine derivatives using various 2-amino-aralkyl alcohols.

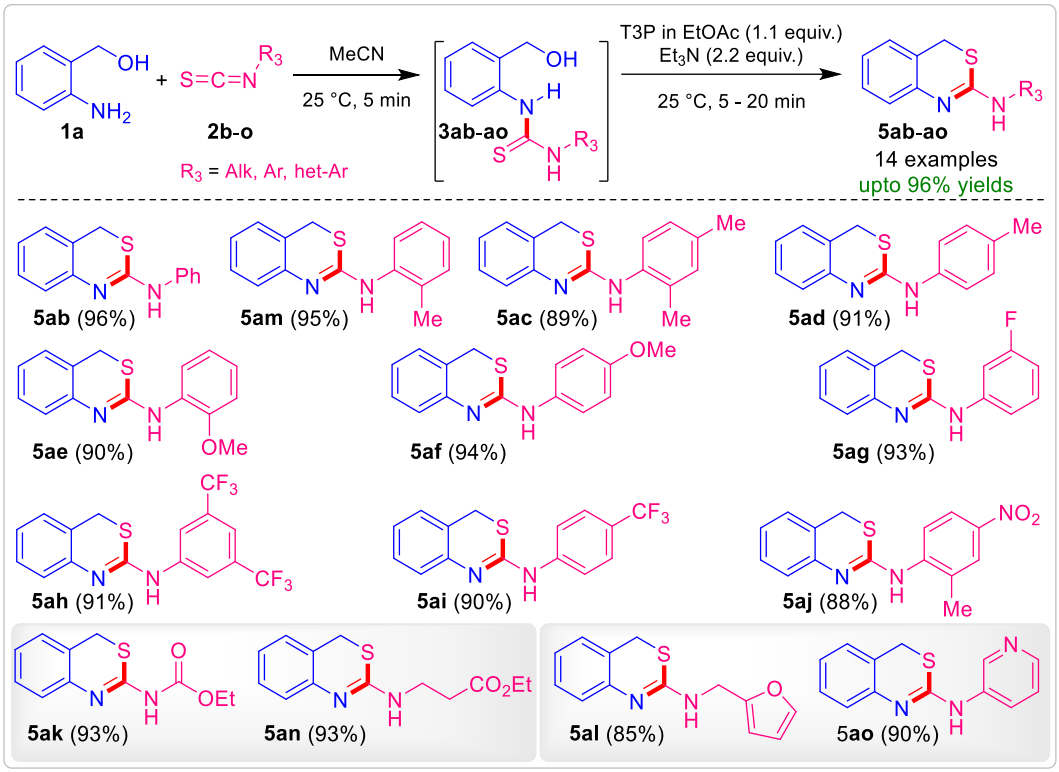


Scheme 12: Substrate scope for the synthesis of 1,3-benzoxazine derivatives using various isothiocyanates

The T3P mediated reaction conditions were investigated for the synthesis of 1,3-benzothiazine derivatives. It was observed that the developed method employed successfully on the varieties of 2-aminobenzyl alcohols (1a-i) and benzoyl isothiocyanate (2a) to obtain the desired 1,3-benzothiazine derivatives (5aa-ia) (Scheme 4).

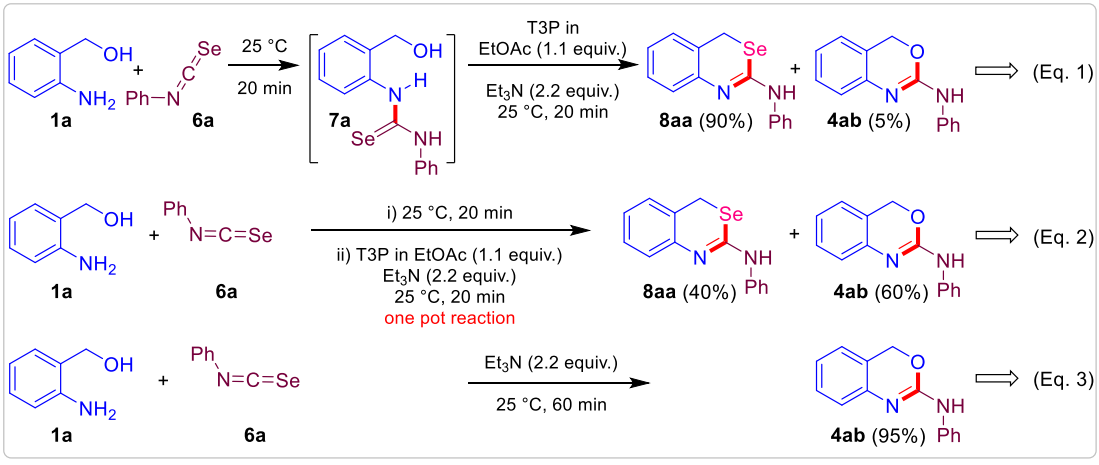


Scheme 13: Substrate scope of 2-N-substituted-1,3 benzothiazine derivatives.



Scheme 14: Substrate Scope of 2-N substituted-1,3 benzothiazine derivatives using isothiocyanates.

To identify the further scope of the developed transformation, the reaction between 2-aminobenzylalcohol (**1a**) and phenyl isoselenocyanate (**6a**) was performed under the optimized conditions (Scheme 6).



Scheme 15: Substrate Scope of 2-N substituted-1,3 benzothiazine derivatives using isoselenocyanates.

Crystal structure of 4fa:

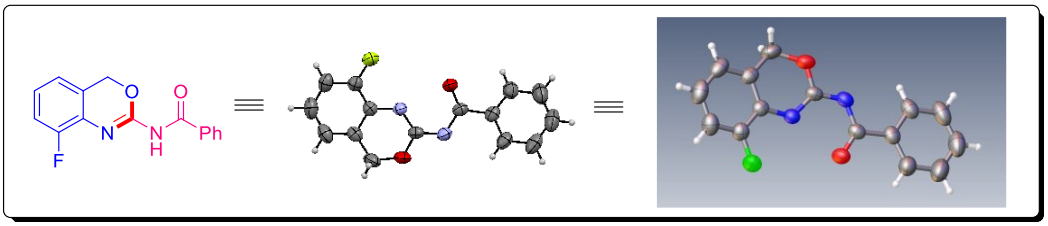


Figure 6: ORTEP diagrams of 4fa (CCDC: 1937631)

Crystal structure of 5fa:

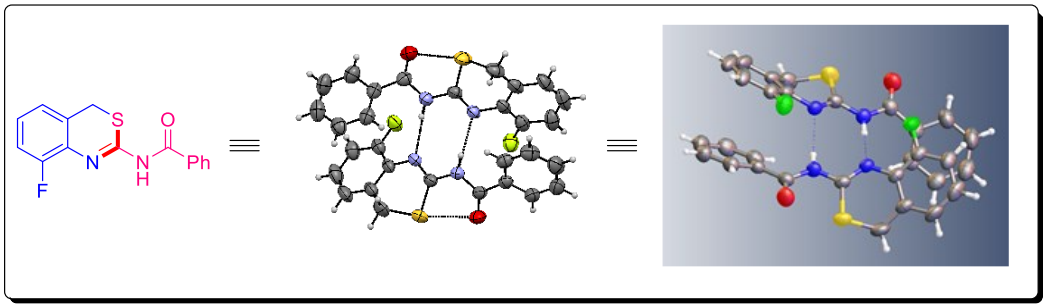
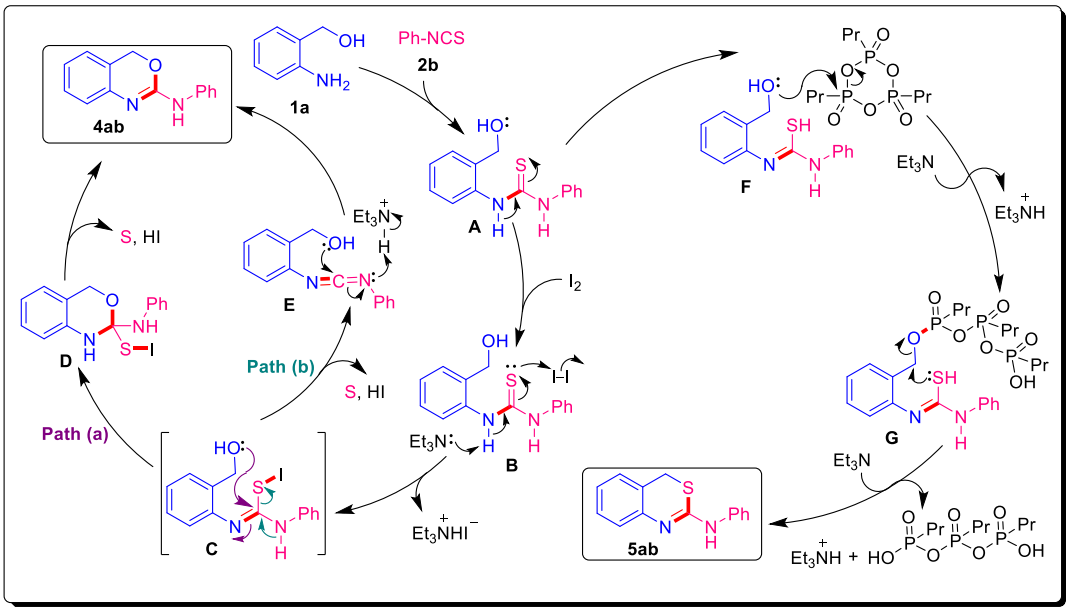


Figure 7: ORTEP diagrams of 5fa (CCDC: 1937629)

4.2.1 Plausible reaction mechanism:



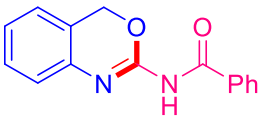
Scheme 16: Mechanism of synthesis of 1,3-benzoxazine and 1,3-benzothiazine.

The initial step of the reaction would follow the generation of intermediate **B** from the reaction between 2-aminobenzyl alcohol (**1a**) and

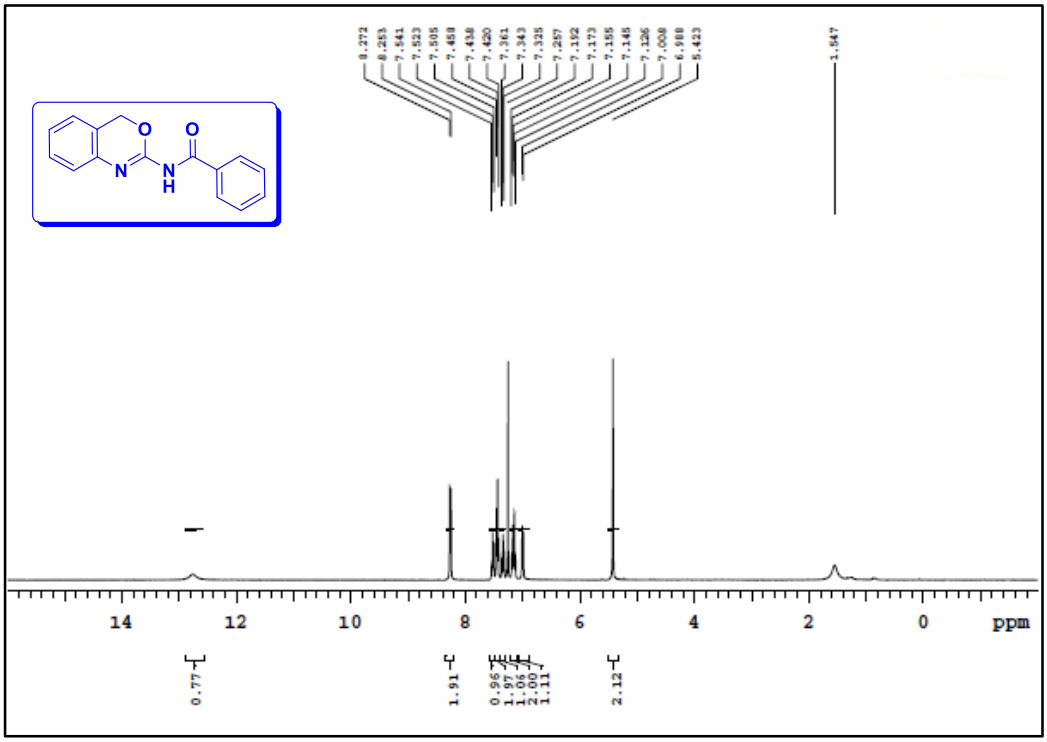
phenyl isothiocyanate (**2a**) followed by the nucleophilic attack of the sulfur atom of **B** on to the molecular iodine leading to the formation of intermediate **C**. The Intermediate **C** then delivers the desired products **4ab** and **5ab** *via* two different reaction pathways. In path (a), the intermediate **C** undergoes intramolecular cyclization to give 1,3-benzoxazine (**4ab**). Another potential route could be the formation of carbodiimide intermediate **E**, which delivers the corresponding 1,3-benzoxozine (**4ab**) (path b). On the other hand, the plausible pathway for the formation of 1,3-benzothiazine can be suggested (Scheme 7) based on literature evidence.[27] The catalytic reaction involves the activation of thiourea moiety **A** by T3P to leading to the formation of intermediate **G**. The next step in the suggested mechanism involves the intramolecular nucleophilic attack of thiol group on to the T3P bound carbon to furnish the corresponding 1,3-benzothiazines (**5ab**).

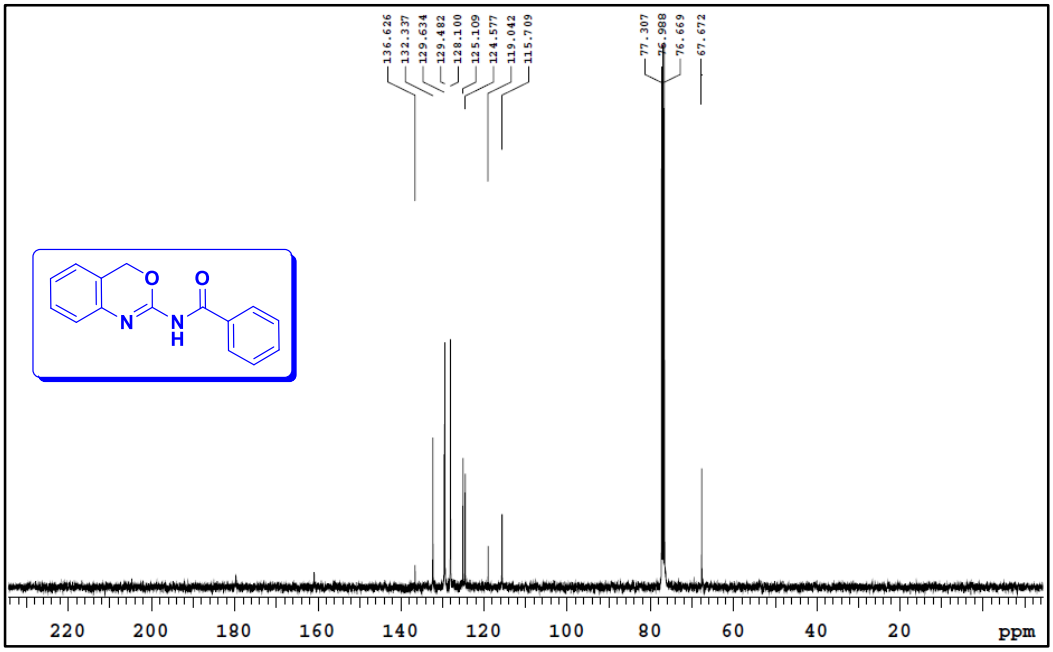
4.2.2 Spectral Data Analysis:

***N*-(4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4aa)**



The reactions between 2-aminobenzyl alcohol **1a** (1.0 mmol, 123 mg), benzoyl isothiocyanate **2a** (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide **4aa** in 98% (247 mg) yield as white solid.


8.272
8.253
7.541
7.523
7.505
7.459
7.438
7.420
7.361
7.343
7.325
7.257
7.152
7.173
7.155
7.145
7.126
7.008
6.988
5.423
1.547
14
12
10
8
6
4
2
0
ppm
0.77
1.91
0.96
1.97
1.06
2.00
1.11
2.12


136.626
132.337
129.634
129.482
128.100
125.109
124.577
119.042
115.709
77.307
76.988
76.669
67.672
220
200
180
160
140
120
100
80
60
40
20
ppm

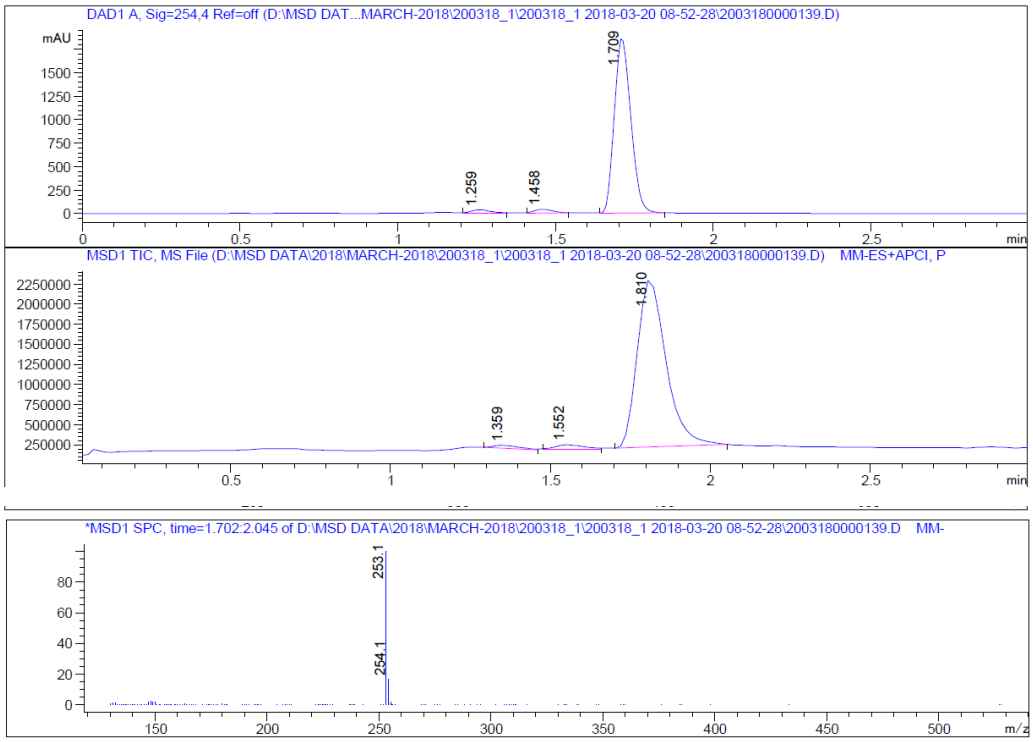
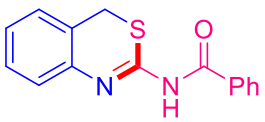


Figure 7. ^{1}H (400 MHz), $^{13}C\{^{1}H\}$ (100 MHz) NMR spectra of **4aa** in $CDCl_3$ and LC-MS in Acetonitrile.

White solid; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 97:3); **Yield**: 247 mg (98%); **m.p** = 126 - 127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.78 (br, 1H), 8.26 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.19 - 7.12 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.42 (s, 2H) ppm; **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ = 179.8, 161.2, 136.6, 132.3, 129.6, 129.4, 128.1, 125.1, 124.5, 119.0, 115.7, 67.6 ppm; **MS** (APCI): $[M + 1]^+$ = 253.1 (95.83%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{13}N_2O_2$: 253.0977; found: 253.0974.

N-(4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5aa)



The reactions between 2-aminobenzyl alcohol **1a** (1.0 mmol, 123 mg), benzoyl isothiocyanate **2a** (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg),

T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide **5aa** in 98% (263 mg) yield as white solid.

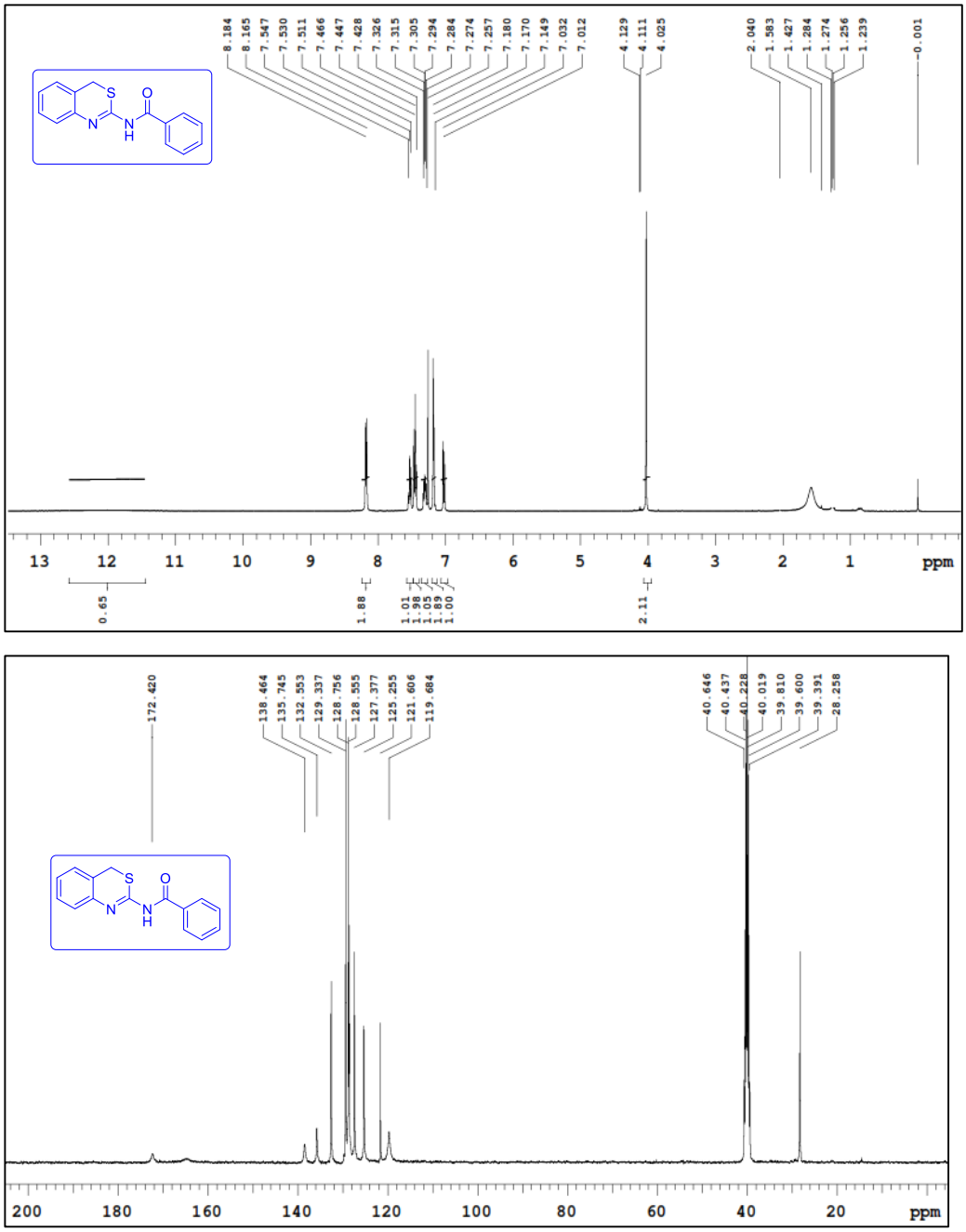


Figure 8. ^{1}H (400 MHz), $^{13}C\{^{1}H\}$ (100 MHz) NMR spectra of **5aa** in $CDCl_3$ and DMSO-d_6 respectively.

White solid; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 87:13); **Yield**: 263 mg (98%); **m.p** = 123 - 124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.0 (bs, 1H), 8.17 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.32 - 7.27 (m, 1H), 7.17 (d, *J* = 4.0 Hz, 2H), 7. 2 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 172.4, 164.5, 138.4, 135.7, 132.5, 129.3, 128.7, 128.5, 127.3, 125.2, 121.6, 119.6, 28.2 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{13}N_2OS$: 269.0748; found: 269.0751.

4.3 Conclusions

In summary, 2-*N*-substituted 1,3-benzoxazines were synthesized in moderate to excellent yields *via* a simple one-pot two-step reaction involving the reaction of 2-aminobenzyl alcohols with isothiocyanates in the presence of molecular iodine and base under short and mild reaction conditions. Whereas the synthesis of 2-*N* substituted 1,3-benzothiazines were synthesized in the presence of T3P reagent and base under mild reaction conditions. In case of benzoxazine molecular iodine promoted the successful dehydrosulfurization of thiourea by releasing elemental sulphur. This is the first example for the synthesis of 2-amino 4*H*-1,3-Benzoxazines *via* iodine promoted dehydrosulfurization method.

CHAPTER-V: 2-AMINO SUBSTITUTED 1,3 BENZOTHIAZINOES & 2 ARYL SUBSTITUTED 1,3 BENZOTHIAZINOES

This chapter describes the introduction, results, discussion and conclusion for the synthesis of 2-amino and 2-aryl substituted 1,3 benzothiazinones.

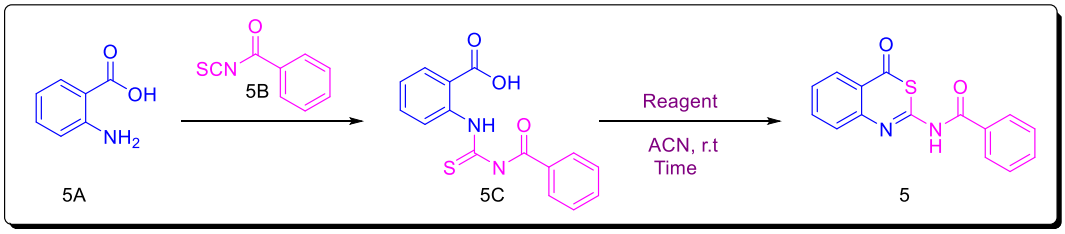
5.1 Introduction

The available literature for the synthesis of 2-Substituted 1, 3 benzothiazenones follow a twostep synthetic route wherein first the corresponding thiourea are formed and then treated in harsh conditions [(2)] like H_2SO_4, Ac_2O to yield the desired benzothiazinones. 2-amino substituted 1, 3 benzothiazenes are synthesized in a three step process wherein tolyl isothiocyanates are converted to the corresponding benzyl bromides followed by treating with pyridine to form pyridinium salts and then heating in DMF [(3)] to get the products. 2-aryl, hetroaryl, alkyl substituted are synthesized following two step synthesis wherein the 2-amino benzyl alcohols are converted to corresponding 2- amino benzyl halides treating with $SOCl_2$ at 110° C and then treating with an appropriate thiobenzamide [(4)] to give the product. Alternatively bis-1,3-Benzenediol, 4,4'-(sulfinyldicarbonothioyl) are first prepared and then treated with 2-amino benzyl alcohols in methanol [(5)] to yield the products. All the above mentioned literature reports employ multistep synthesis, harsh conditions and long reactivity times. So the need to develop a simple and efficient synthetic methodology is inevitable.

5.2 Results and Discussion

To scout suitable reaction conditions, anthranilic acid was treated with benzolyisothiocyanate to form the corresponding thiourea and then treated with different dehydrating, carbodiimides, uranium and phosphonium

based reagents in the presence of various solvents at different temperatures. The results are depicted in the following table.



Reagent	Conversion (20 min) [c]	Product 4 (%) [b]
-	0	0
EDC.HCl	**>99**	**96**
DCC	>99	95
BOP	>99	70
PyBOP	>99	80
HATU	>99	60

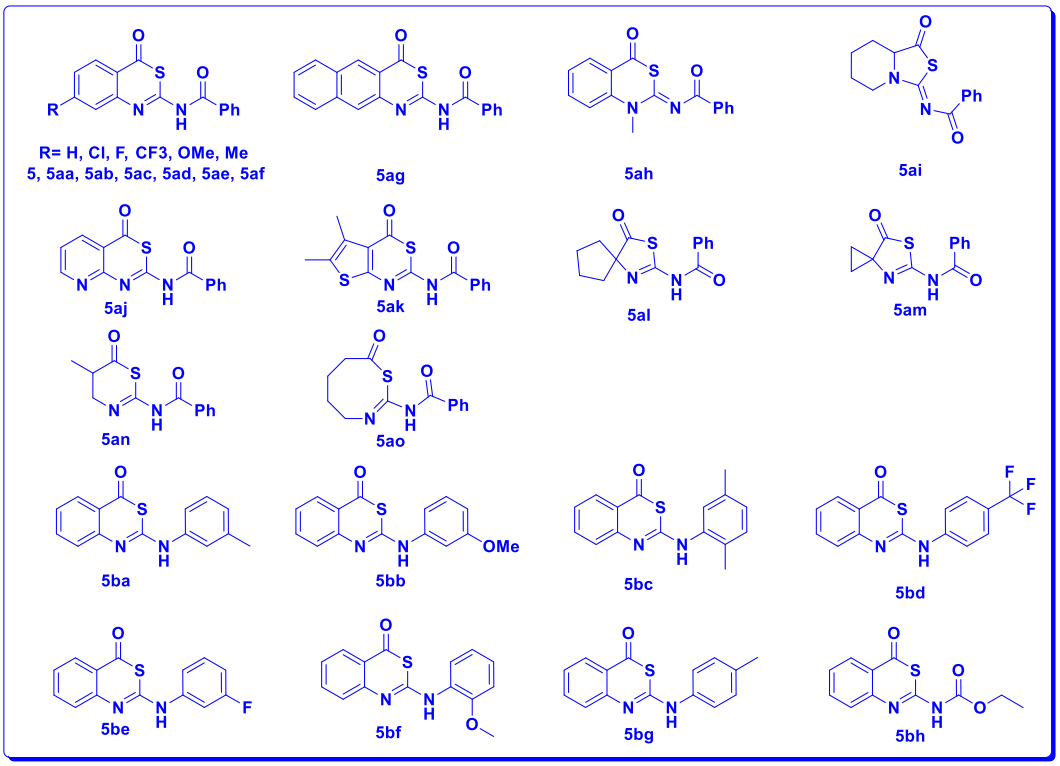
Reagent	Temp (°C)	Solvent	Product 4 (%) [b]
EDC.HCl	23° C	DCM	90
EDC.HCl	**23° C**	**ACN**	**96**
EDC.HCl	50° C	ACN	95
EDC.HCl	100°	ACN	70
EDC.HCl	23°	THF	80
EDC.HCl	23°	DMF	60

[a] reaction (1&**2** :1 equiv; reagent: 1.1 equiv; Et_3N: 1.5 eq

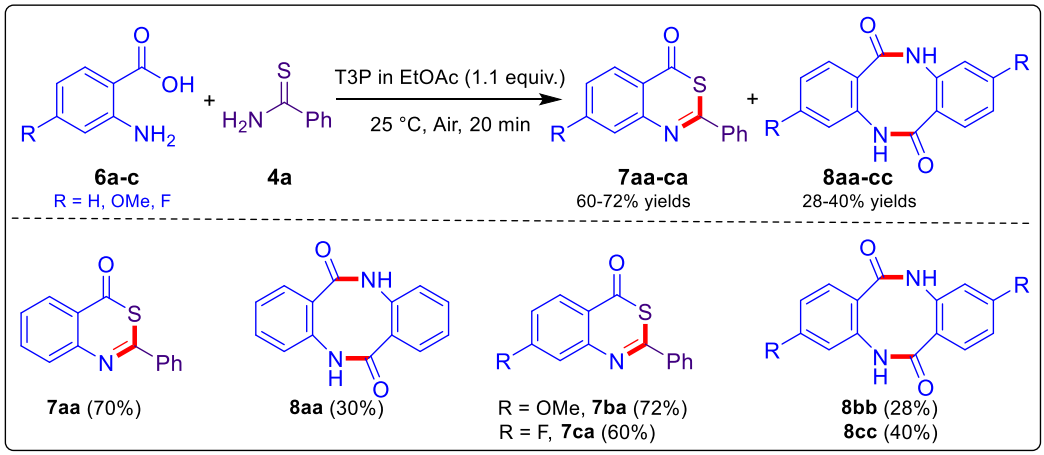
[b] isolated yield

[c] monitored by LCMS

The scope of the reaction was further expanded with different anthranilic acids and different isothiocyanates and the results are shown in the below table.



Scheme 17: Substrate Scope of 2-N substituted-1,3 benzothiazinone derivatives using various isothiocyanates and anthranilic acids/terminal Amino acids.



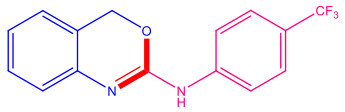
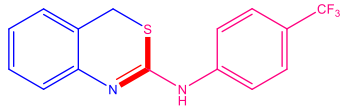
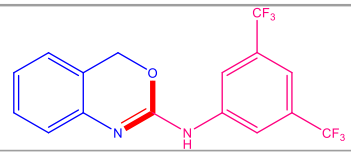
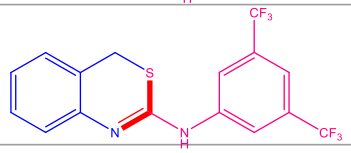
Scheme 18: Scope of the reaction using thiobenzamides.

CHAPTER-VI: ANTIBACTERIAL ACTIVITY OF BENZOTHIAZINONES & MOLECULAR DOCKING STUDY OF BENZOTHIAZINES AND BENZOXAZINES AGAINST THE HUMAN TNKS-1 ENZYME

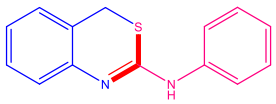
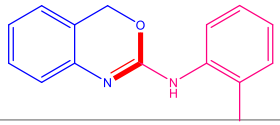
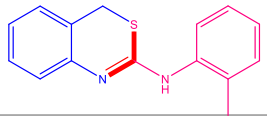
This chapter describes the introduction, antibacterial activity studies of 1,3 benzothiazinones, modelling studies of 1,3 benzothiazines and benzoxazines.

ANTIBACTERIAL ACTIVITY:

Few of the benzothiazinones synthesized were tested for their in vitro growth inhibitory activity against different bacteria. The bacterial strains used were Bacillus subtilis ATCC 6633 and Staphylococcus aureus ATCC 6538 as Gram-positive bacteria and Salmonella typhimurium ATCC 14028 (Salmonella enterica) and Proteus vulgaris ATCC 13315 as Gram-negative bacteria. MIC and MBC (µg/mL) of selected compounds and streptomycin

Compound	B. subtilis		S. aureus		P. vulgaris		S. typhimurium	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
	>800	>800	>800	>800	>800	>800	>800	>800
	>800	>800	>800	>800	>800	>800	>800	>800
	>800	>800	>800	>800	>800	>800	>800	>800
	>800	>800	>800	>800	>800	>800	>800	>800
Streptomycin	15	15	36	10	10	110	110	110

against Gram-positive bacteria B. subtilis, S. aureus and Gram-negative bacteria P. vulgaris, and S. typhimurium

Compound	B. subtilis		S. aureus		P. vulgaris		S. typhimurium	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
	>800	>800	>800	>800	>800	>800	>800	>800
	>800	>800	>800	>800	>800	>800	>800	>800
	>800	>800	>800	>800	>800	>800	>800	>800
	>800	>800	>800	>800	>800	>800	>800	>800
Streptomycin	15	15	36	10	10	110	110	110

MOLECULAR DOCKING STUDY:

Colorectal cancer (CRC) is one of the deadliest forms of disease in the modern era. According to the recent report, CRC holds third rank in terms of incidence but second in term of mortality globally.[43] Presently, several drugs, such as small molecules (5-fluorouracil, capecitabine),[44] Human monoclonal antibodies (bevacizumab, cetuximab, panitumumab),[45] recombinant protein (afliberecpt),[19/46] etc., working through numerous pharmacological pathways, are either in clinical practices or undergoing clinical trials. Although enormous effort is already made to combat CRC, deadly cytotoxicity of the prescribed drugs and prevailing drug resistant cancer are the global threat for the patients suffering in fatal CRC, and warrants the search for new drugs acting through novel mechanism.[47]

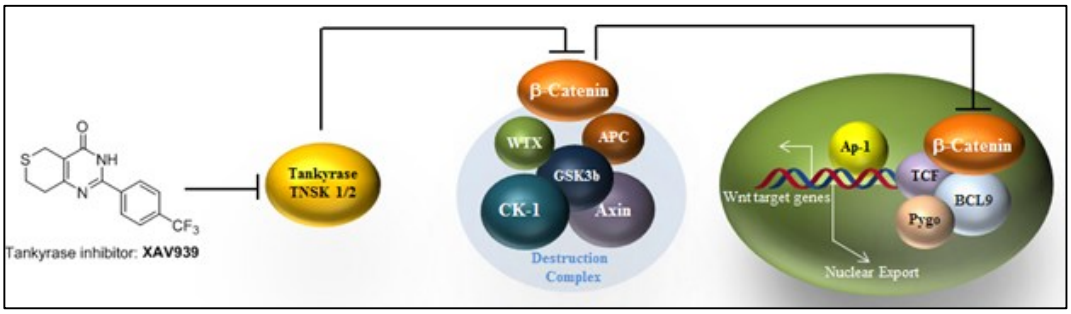


Figure 9: Molecular docking study of oxazine and thiazine derivatives

Tankyrase 1 (TNKS-1) and Tankyrase 2 (TNKS-2) belong to the poly ADP-ribose polymerase (PARP) family,[48] and are involved in telomere maintenance, WNT signaling and mitosis. WNT pathway controls cell proliferation *via* β-catenin which is overexpressed in case of over-functioning or non-degradation of β-catenin; this causes accumulation of β-catenin in cytoplasm and its subsequent translocation into the nucleus where it acts as transcriptional factor in CRC development.[49] In normal physiological condition β-catenin degrades in cytoplasm by Axins, Adenomatosis polyposis coils (APC), phosphatase, and glycogen synthase kinase (Figure 2). As soon as WNT binds to Frizzled protein receptor, the destruction complex function gets disturbed, which leads to accumulation of β-catenin and localize into nucleus consequently trigger the CRC.[50] The small organic molecule XAV939 is found to be a potent inhibitor of TNKS-1 and TNKS-2 with IC_{50} values 11 and 4 nM, respectively.[51] Since our mild catalytic methodology gave us a diversified library of 2-amino-1,3-benzoxazines and 2-amino-1,3-benzothiazines which possess similarity with **XAV939** in terms of overall similar pharmacophoric patterns and the topology, we assumed that our synthesized novel compounds could bind in a similar or better fashion, as compared with **XAV939**. To resolute the possibility of new chemical entity (NCE) for the future CRC chemotherapy, herein we report the results of molecular docking study on 2-amino-1,3-benzoxazines and 2-amino-1,3-benzothiazines derivatives, synthesized by the method described in this paper, into the active site of TNKS-1 enzyme.

Molecular docking study of oxazine and thiazine derivatives have revealed few of them (**4ai**, **5ai**, **4ah** and **5ah**) to have better binding capabilities over XAV939 into the active site of TNKS-1 enzyme. Certainly, this *in-silico* study opens up a new research avenue for the construction of NCEs in CRC chemotherapeutics.

Table 3. Summary of docking results for selected ligands and XAV939 into the active site of TNKS-1 enzyme.

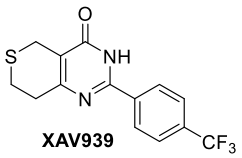
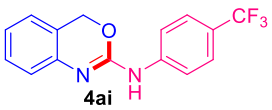
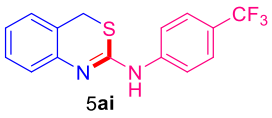
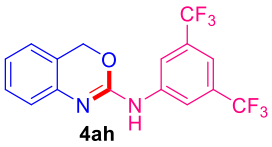
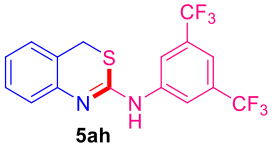
Entry	Structure	Glide gscore[a] (kcal.mol^{-1})	Protein-Ligand Interaction		
			H-bonds	π-π interaction	Hydrophobic
1	 XAV939	-10.325[b]	GLY1185, SER1221	TYR1224	PRO1187, PHE1188, TYR1203, TYR1213, PHE1214, ALA1215, TYR1224
2	 4ai	-10.837	GLY1185	TYR1224	**PHE1183,** PRO1187, PHE1188, **ALA1202**, TYR1203, **ILE1228**, TYR1213, PHE1214, ALA1215, TYR1224

Table 3. Summary of docking results for selected ligands and XAV939 into the active site of TNKS-1 enzyme. *(Contd…)*					
Entry	**Structure**	**Glide gscore[a] (kcal.mol^{-1})**	**Protein-Ligand Interaction**		
			H-bonds	**π-π interaction**	**Hydrophobic**
3	 5ai	-10.985	GLY1185	TYR1224, **TYR1203**	**PHE1183,** PRO1187, PHE1188, TYR1203, TYR1213, PHE1214, ALA1215, **ILE1228,** TYR1224**, TYR1292**
4	 4ah	-11.615	GLY1185	TYR1224	**PHE1183,** PRO1187, PHE1188, **ILE1192, ALA1202**, TYR1203, **MET1207, ILE1212,** TYR1213, PHE1214, ALA1215, TYR1224, **ILE1228**
5	 5ah	-11.926	GLY1185	TYR1224	**PHE1183,** PRO1187, PHE1188, **ILE1192, ALA1202**, TYR1203, **MET1207, ILE1212,** TYR1213, PHE1214, ALA1215, TYR1224, **ILE1228**
[a]Determined by standard precision (SP) method. [b]Score obtained after rescoring the experimentally determined bioactive conformation of XAV939 bound with TNKS-1 (PDB ID: 3UH4).					

The docking study revealed that like the control **XAV939 (**Table 2: Entry **1** and Figure **3a)**, new molecules displayed similar binding with TNKS-1 in terms of overall location of the putative bioactive conformations and various types of interactions, including H-bonding, electrostatic, hydrophilic, hydrophobic and π-π stacking interactions. In case of benzoxazine class of compounds **4ai** and **5ai**, H-bonding was observed between ligand (ring O and NH) and GLY1185, and oxazine part was engaged in π-π stacking interaction with TYR1224. Furthermore, these molecules were engaged in hydrophobic interactions with various corresponding class of amino acids, as also found in co-crystal X-ray structure of **XAV939** bound TNKS-1 (Table 2: Entry **2**, **3** and Figure **3b**, **3c**). On the other hand, benzothiazine class of compounds **4ah** and **5ah** showed H-bonding with GLY1185 C=O, π-π stacking interaction with TYR1224, and hydrophobic interactions with several amino acids lining the binding site (Table 2: Entry **4**, **5** and Figure **3d**, **3e**). In terms of docking scores (glide gscore), benzothiazine class of compounds **4ah** and **5ah** scored better than benzoxazine class of compounds **4ai** and **5ai**, suggesting the favorable role of ring flexibility (thiazine vs oxazine) for better binding with TNKS-1 and thus for potent inhibition.

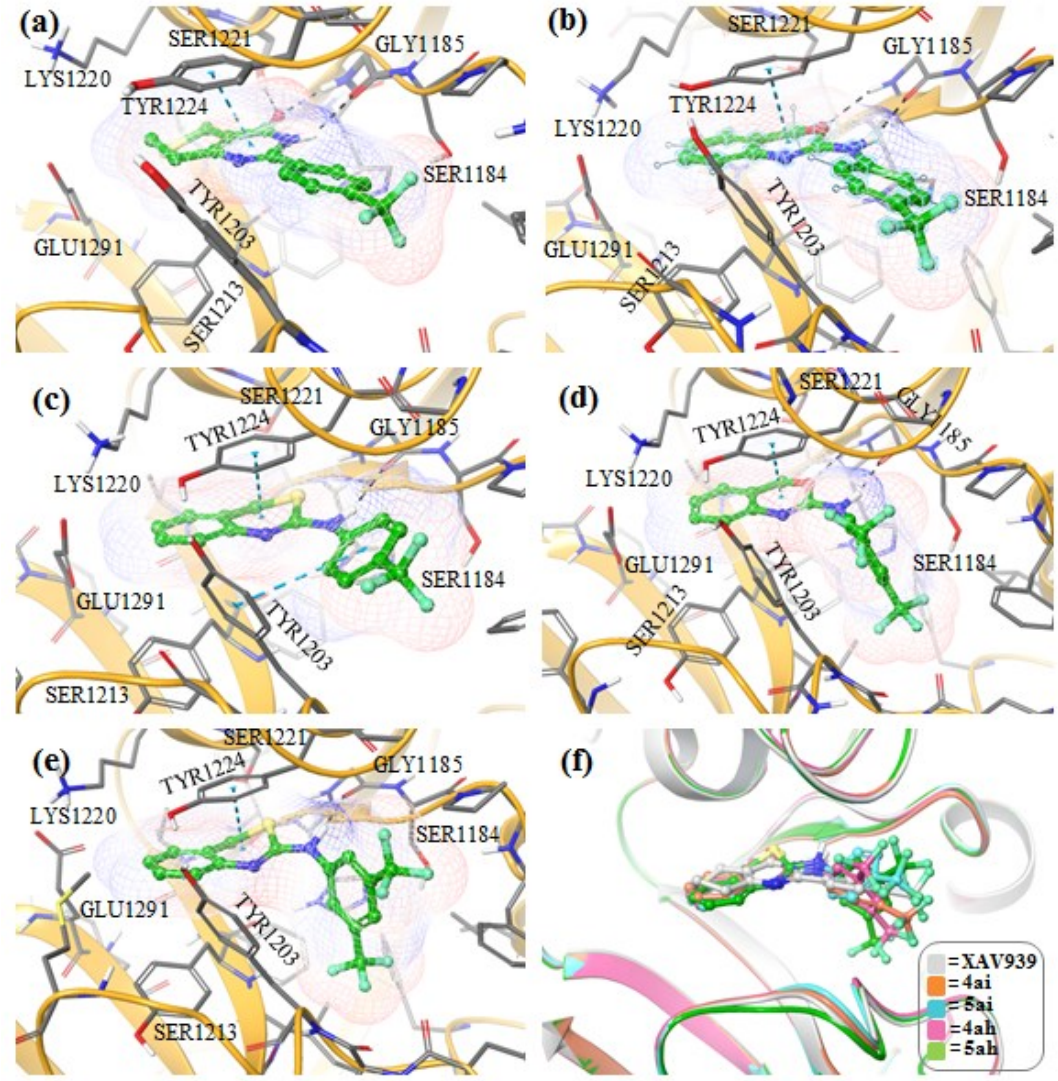


Figure 10. (a-e) Depiction of interaction profile of: (a) **XAV939**, (b) **4ai**; (c) **5ai**, (d) **4ah**; and (e) **5ah** at the active site of TNKS-1. Ligands are represented as ball-and-stick with green carbon. Binding site amino acids are represented as tube with grey carbon. Protein is represented in cartoon form. (f) Overlay of predicted binding poses of selected ligands into the active site of TNKS-1.

CHAPTER VII: SUMMARY & CONCLUSIONS

In conclusion, we have developed a facile protocol for the synthesis of 1,3-benzoselenazines and 1,3-benzothiazines from aryl/heteroaryl-alkyl alcohols and selenocarboxamides or thiocarboxamides to obtain the desired products in excellent yields. The developed method was successful in overcoming the drawbacks associated with the previous reported protocols in terms of reaction conditions, substrates and the library of the products. All investigated examples proved to be general irrespective of the electronic nature of substituents on the substrates. The current protocol relies on the readily available inexpensive substrates under mild conditions at room temperature and minimum reaction time to synthesize a broad range of structurally diversified rarely explored 1,3-benzoselenazines and 1,3-benzothiazines.

2-*N*-substituted 1,3-benzoxazines were synthesized in moderate to excellent yields *via* a simple one-pot two-step reaction involving the reaction of 2-aminobenzyl alcohols with isothiocyanates in the presence of molecular iodine and base under short and mild reaction conditions. Whereas the synthesis of 2-*N* substituted 1,3-benzothiazines were synthesized in the presence of T3P reagent and base under mild reaction conditions. In case of benzoxazine molecular iodine promoted the successful dehydrosulfurization of thiourea by releasing elemental sulphur. This is the first example for the synthesis of 2-amino 4*H*-1,3-Benzoxazines *via* iodine promoted dehydrosulfurization method. Although the antibacterial activities of benzothiazinones are not fruitful, molecular docking study using the above synthesized library of oxazine and thiazine derivatives have revealed few of them to have better binding capabilities over XAV939 into the active site of TNKS-1 enzyme.

References

1 Thomas C. Kuehler, Jan Fryklund, Nils-ke Bergman, Jessica Weilitz, Adrian Lee, Haakan Larsson. Structure-Activity Relationship of Omeprazole and Analogs as Helicobacter pylori Urease Inhibitors. *Journal of Medicinal Chemistry* **1995**, 38, 25, 4906-4916.

2 Hamad *A Al-Khamees*, Said *M Bayomi*, Hesham *A* Kandil, and Kamal E. *H* El-Tahir. Synthesis and pharmacological screening of *a* new series of 3-(4-anti-pyryl)-2-arylthiazolidin-4-ones. *European Journal of Medicinal Chemistry* 1990, Volume 25, Issue 2, 103-106.

3 Nicholas *K. Terrett,* Mark *Gardner,* David W. Gordon, Ryszard J. Kobylecki, John Steele Combinatorial synthesis-the design of compound libraries and their application to drug discovery. *Tetrahedron* 1995, Volume 51, Issue 30, 8135-8173.

4 Mar Gómez-Gallego*,* María *J* Mancheño*,* Miguel *A* Sierra*.* Non-Classical Polycyclic β-Lactams. *Tetrahedron* 2000, Volume 56, Issue 32, 5743-5774.

5 John Krapcho, Chester F. Turk. 4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2H-1,4-benzothiazine and related compounds. New class of antiinflammatory agents. *Journal of Medicinal Chemistry* **1973**, 16, 7, 776-779**.**

6 Lee EB, Kwon SK, Kim SG. Synthesis and analgesic and anti-inflammatory activities of 1,2-benzothiazine derivatives. *Arch Pharm Res.* 1999, Volume 22, Issue 1, 44-47

7 K. Scherlach, H. W. Nützmann, V. Schroeckh, H.-M. Dahse, A. A. Brakhage and C. Hertweck. Cytotoxic Pheofungins from an

Engineered Fungus Impaired in Posttranslational Protein Modification. *Angew. Chem., Int. Ed.* 2011, 50, 9843.

8 J. Matysiak. Synthesis and antiproliferative activity of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles. *Bioorg. Med. Chem.* 2006, 14, 2613.

9 Violetta Cecchetti, Arnaldo Fravolini, Pier Giuseppe Pagella, Angela Savino, Oriana Tabarrini. Quinolinecarboxylic acids. 3. Synthesis and antibacterial evaluation of 2-substituted 7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzothiazine-6-carboxylic acids related to rufloxacin. *Journal of Medicinal Chemistry,* **1993**, 36, 22, 3449-3454.

10 M. B. Deshmukh, A. R. Mulik and S. D. Desai. Synthesis of Some New 2-Methyl -1,4-benzothiazine-3(1*H*)- one Derivatives as Potential Vasodilators. *E-J. Chem.* 2004, 1, 206.

11 V. I. Cohen. A Facile Synthesis of 3,5-Diaryl- and 3,5-Diheteroaryl-1,2,4-selenadiazoles. *Synthesis* 1978, 768;

12 J. Krapcho and C. F. Turk. 4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2H-1,4-benzothiazine and related compounds. New class of antiinflammatory agents. *J. Med. Chem.* 1973, 16, 776.

13 D. Y. Direnko, Y. B. Drevko and B. I. Drevko. The Synthesis of New Organoselenium Heterocyclic Compounds: 2-aryl-4-phenyl-5,6,7,8-tetrahydro-4H-selenochromenes. *J. Chin. Chem. Soc.* 2015, 62, 1068.

14 P. Sun, M. Jiang, W. Wei, Y. Min, W. Zhang, W. Li, D. Yang and H. Wang. Copper-Catalyzed Selenylation of Imidazo[1,2-*a*]pyridines with Selenium Powder via a Radical Pathway. *J. Org. Chem.* 2017, 82, 2906.

15 J. Szabó. 1,3-Benzothiazines (review). *Chem. Heterocycl. Compd.* 1979, 15, 239.

16 M. Soriano-Garcia. Organoselenium Compounds as Potential Therapeutic and Chemopreventive Agents: A Review. *Current Medicinal Chemistry* 2004, Volume 11, Issue 12, 1657 – 1669.

17 M. Parnham and E. Graf, Pharmacology of Synthetic Organic Selenium Compounds. *Progrès des recherches pharmaceutiques, Birkhäuser Basel*. 1991, vol. 36, p. 9.

18 R. Naithani. Organoselenium Compounds in Cancer Chemoprevention**.** *Mini-Rev. Med. Chem.* 2008, 8, 657.

19 X. Sun, Y. Zhong, H. Luo and Y. Yang. Selenium-Containing Polysaccharide-Protein Complex in Se-Enriched *Ulva fasciata* Induces Mitochondria-Mediated Apoptosis in A549 Human Lung Cancer Cells. *Mar. Drugs.* 2017, 15, 215.

20 T. Ogunmoyole, J. B. T. Rocha, A. E. Okoronkwo and I. J. Kade. Altered pH homeostasis modulates the glutathione peroxidase mimics and other antioxidant properties of diphenyl diselenide. *Chem.-Biol. Interact.* 2009, 182, 106.

21 Michio Iwaoka, Shuji Tomoda. First Observation of a C-H...Se "Hydrogen Bond". *Journal of the American Chemical Society*. **1994**, 116, 10, 4463-4464.

22 Mar *Gómez-Gallego,* María *J Mancheño*, Miguel *A Sierra.* Non-Classical Polycyclic β-Lactams. *Tetrahedron*, Volume 56, Issue 32, 2000, 5743-5774.

23 Brown, A. D.; Powers, J. C. Rates of thrombin acylation and deacylation upon reaction with low molecular weight acylating agents,

carbamylating agents and carbonylating agents. *Bioorg. Med. Chem*. 1995, 3, 1091-1097.

24 Besson, T.; Rees, C. W.; Cottenceau, G.; Pons, A. M. Antimicrobial evaluation of 3,1- benzoxazin-4-ones, 3,1-benzothiazin-4-ones, 4-alkoxyquinazolin-2-carbonitriles and N-arylimino1,2,3-dithiazoles. *Bioorg. Med. Chem. Lett*. 1996, 6, 2343-2348.

25 Michael Gütschow, Miriam Schlenk, Jürgen Gäb, Minka Paskaleva, Mohamad Weaam Alnouri, Silvia Scolari, Jamshed Iqbal, Christa E. Müller. Benzothiazinones: A Novel Class of Adenosine Receptor Antagonists Structurally Unrelated to Xanthine and Adenine Derivatives. *J. Med. Chem.* 2012, 55, 73, 331-3341.

26 Anne Stößel, Miriam Schlenk, Sonja Hinz, Petra Küppers, Jag Heer, Michael Gütschow, Christa, E. Müller. Dual Targeting of Adenosine A_{2A} Receptors and Monoamine Oxidase B by 4*H*-3,1-Benzothiazin-4-ones. *J. Med. Chem.* 2013, 56, 11, 4580-4596.

27 M. C. Fong, R. W. Gable and C. H. Schiesser. 3-Phenyl-1,3(4*H*)-benzoselenazine-2,4(3*H*)-dione. *Acta. Crystallogr, Sect. C: Cryst. Struct. Commun*. 1995, 51, 1333.

28 S. W. Wright. One - pot synthesis of novel sulfur and selenium heterocycles by directed ortho-lithiatio. *J. Heterocycl. Chem.* 2001, 38, 723.

29 R. Sathunuru and E. Biehl. Facile synthesis of 4*H*-naphtho[2,3-*e*] derivatives of 1,3-thiazines and 1,3-selenazines and naphtho[2',3':4,5] derivatives of selenolo[2,3-*b*]pyridines and thieno[2,3-*b*]pyridines *via* 2,3-didehydronaphthalene. *ARKIVOC* 2004, xiv, 51.

30 A. Dondoni, A. Battaglia and P. Giorgianni. Selectivity in ketenimine-thioketone cycloadditions-1,4- and 1,2-Addition pathways and the

synthesis of 4H-3,1-benzothiazines, 2-iminothietanes, and thioacrylamides. *J. Org. Chem.* 1980, 45, 3766.

31 T. Nishio. Reaction of (1,ω)-*N*-Acylamino Alcohols with Lawesson's Reagent: Synthesis of Sulfur-Containing Heterocycles. J. Org. Chem., 1997, 62, 1106;

32 S. I. El-Desoky, E. M. Kandeel, A. H. Abd-El-Rahman and R. R. Schmidt. Synthesis and reactions of 4*H*-3,1-benzothiazines. *J. Heterocycl. Chem.* 1999, 36, 153.

33 Péter Csomós, Lajos Fodor, Gábor Bernáth, Jari Sinkkonen, Kalevi Pihlaja. Novel β-lactam condensed 3-thiaquinolines: an efficient synthesis and structural characterization. *Tetrahedron 2008, Volume 64, Issue 6, 1002-1011.*

34 L. Fodor, G. Bernáth, J. Sinkkonen and K. Pihlaja. Synthesis and structural characterisation of 4*H*-1,3-benzothiazine derivatives. *J. Heterocycl. Chem.* 2002, 39, 927.

35 Cédric Spitz, Jean-François Lohier, Vincent Reboul, Patrick Metzner. Catalytic Generation of Cesium Acetylide by CsF: Synthesis of 1,3-Benzothiazines from Cyclic Sulfenamides. *Organic Letters* a, 2011, 13, 2776-2779.

36 G. Qiu, Y. Hu, Q. Ding, Y. Peng, X. Hu and J. Wu. Synthesis of 4-methylene-4*H*-benzo[*d*][1,3]thiazines *via* a tandem reaction of 1-(2-alkynylphenyl)ketoximes with Lawesson's reagent**.** *Chem.Communa.* 2011, 47, 9708.

37 William P. Unsworth, Christiana Kitsiou, Richard J. K. Taylor. Direct Imine Acylation: Rapid Access to Diverse Heterocyclic Scaffolds. *Organic Letters* **2013** 15, 2, 258-261**.**

38 Hui-Hong Wang, Tao Shi, Wei-Wei Gao, Hong-Hua Zhang, Yong-Qianga Wang, Jun-Fang, Li Yong-Sheng, Hou Jin-Hong, Chen Xue Peng and Zhen Wang. Double 1,4-addition of (thio)salicylamides/thiosalicylic acids with propiolate derivatives: a direct, general synthesis of diverse heterocyclic scaffolds. *Org.Biomol.Chem*. 2017, 15, 8013.

39 Jie, H.; Yong, Y.; Lu, H.; ZhiGanga, Y.; Fan, X.; Qi, S. Tandem addition-cyclization reaction catalyzed by ytterbium chloride: An efficient one-step synthesis of 2-amino-4*H*-3,1-benzothiazine. *Chin. Sci. Bull.* 2013, *58*, 717.

40 Larksarp, C.; Alper, H. Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Heterocumulenes: Regioselective Preparation of 4(3*H*)-Quinazolinone Derivatives. *J. Org. Chem*. 2000, *65*, 2773.

41 Ghosh, H.; Yella, R.; Nath, J.; Patel. B. K. Desulfurization Mediated by Hypervalent Iodine(III): A Novel Strategy for the Construction of Heterocycles. *Eur. J. Org. Chem*. 2008, 6189.

42 KamaI, A.; Sattur, P. K. Catalase-mediated cyclization: Synthesis of 3-allyl-4-imino substituted 2(1*H*)-quinazolinones and 1,3-benzoxazine-2(3*H*)-ones. *Tetrahedron Lett.* 1989, *30*, 1133.

LIST OF PUBLICATIONS

1. V.P. Rama Kishore Putta, Raghuram Gujjarappa, Ujjawal Tyagi, Prasad P. Pujar, Chandi C. Malakar. Metal- and Base-Free Domino Protocol for the Synthesis of 1,3-Benzoselenazines, 1,3-Benzothiazines and Related Scaffolds. *Org. Biomol. Chem.* 2019, 17, 2516–2528
2. V. P. Rama Kishore Putta, Nagaraju Vodnala, Raghuram Gujjarappa, Ujjawal Tyagi, Aakriti Garg, Kuldeep K. Roy, Sreya Gupta, Prasad P. Pujar and Chandi C. Malakar. Reagent-Controlled Divergent Synthesis of 2-Amino-1,3-Benzoxazines and 2-Amino-1,3-Benzothiazines and Docking-based Evaluation against Human Tankyrase-1 Enzyme: *Journal of Organic Chemistry*. **(Accepted, minor revision in progress)**
3. EDCI mediated efficient onepot synthesis of Benzothiazinones from Anthralinilic acids and terminal amonoacids. **(manuscript in progress)**

Apart from the above publications which are part of the thesis, the following publication have been accomplished.

4. The facile and efficient organocatalytic platform for accessing 1,2,4-selenadiazoles and thiadiazoles under aerobic conditions. *Tetrahedron Letters*, Volume 59, Issue 10, 7 March 2018, Pages 904-908.

LIST OF CONFERENCES ATTENDED & ACCEPTED

1. **International Conference on "Drug Discovery India 2017 (Medicinal Chemistry)" held in Le Meridien Bangalore Hotel, Bengaluru on September 14-15, 2017, conducted by SELECT BIO International.**

2. **International Conference on "Medicinal Chemistry And Drug Discovery & Development, India 2019" conducted at Biocon Academy, Bengaluru From March 04th – 09th, 2019, conducted by Biocon academy and ACS Medicinal Chemistry Division.**

3. **Accepted Poster Presentation in International Conference on Emerging Trends in Chemistry from July 12-15, 2019, to be held at IIT-Indore**

4. **Accepted Poster Presentation in 25th CRSI National Symposium in Chemistry CRSI - NSC 25, 19 - 21 July 2019, to be held at IIT-Kanpur**